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Evaluation of educational strategies for hospital antimicrobial stewardship: a multisite approach

Stuart Bond
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**Evaluation of educational strategies
for hospital antimicrobial stewardship:
a multisite approach**

**A thesis submitted in fulfilment of the
requirements for the award of the degree of**

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University of Wollongong

by

Stuart Bond BPharm DipPharmPrac

Faculty of Science, Medicine and Health

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Bond SE, Chubaty AJ, Adhikari S, Miyakis S, Boutlis CS, Yeo WW, Batterham MJ, Dickson C, McMullan BJ, Mostaghim M, Li-Yan Hui S, Clezy KR, and Konecny P (2017). ‘Outcomes of multisite antimicrobial stewardship program implementation with a shared clinical decision support system’, *Journal of Antimicrobial Chemotherapy* (Epub ahead of print), doi: 10.1093/jac.dkx080, Impact factor 4.919 (Chapter 5)

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3. 'Antimicrobial stewardship - the ABCs of implementation'
Melbourne Health Antimicrobial Stewardship Pharmacist workshop,
Melbourne, July 2014
4. 'Building a sustainable stewardship program'
Preventing and Controlling Infection conference, Sydney, September 2014
5. 'Antimicrobials workshop – surgical prophylaxis, urinary tract infection and
community-acquired pneumonia'
Illawarra Pharmacists' Symposium, Wollongong Hospital, November 2014
6. 'Antibiotic surgical prophylaxis - what's new'
Department of Anaesthesia Morbidity and Mortality meeting, Wollongong Hospital,
February 2015
7. 'Community-acquired pneumonia'
Emergency Medicine educational meeting, Wollongong Hospital, May 2015
8. 'How to build antimicrobial stewardship around a local health district'
Strengthening antimicrobial stewardship conference, Sydney, May 2015
9. 'Community-acquired pneumonia 2013 vs. 2014'
Department of Respiratory Medicine educational meeting, Wollongong Hospital,
June 2015

10. 'Orthopaedics/Infectious Diseases update'

Department of Orthopaedic Surgery educational meeting, Wollongong Hospital,
June 2015

11. 'Networked antimicrobial stewardship in regional and rural settings'

National Centre for Antimicrobial Stewardship Seminar, Melbourne, July 2015

12. 'Computer says yes! Evaluating the impact of an antimicrobial stewardship
program supported by clinical software'

Illawarra Shoalhaven Local Health District Research Week, Wollongong Hospital,
November 2015

13. 'Intravenous to oral switch – why bother?'

Nurse education, Wollongong Hospital, April 2016

14. 'Serious games for health professional education'

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Abstract

Introduction

According to the World Health Organisation, antimicrobial resistance (AMR) is one of the major threats to human health in the twenty-first century. Many of the advances of modern medicine, such as cancer treatments and complex surgeries, are being threatened by the development of AMR. Antimicrobial overuse has been associated with the development of AMR. This has resulted in a situation where previously treatable infections can now become life-threatening. To address these risks, antimicrobial stewardship (AMS) has been developed as an important strategy for improving the use of antimicrobials. AMS aims to improve patient outcomes, reduce adverse effects, and alleviate AMR. Most of the available literature on AMS has been derived from single site, metropolitan teaching hospitals with on-site infectious diseases, pharmacy and microbiology support. There remains an evidence gap for AMS strategies that are applicable to non-metropolitan and multisite hospital settings.

The aims of this thesis were threefold: (1) to develop and evaluate educational strategies for improving antimicrobial use in different clinical settings, such as infection prevention, treatment of infection, and side effects of antimicrobial use; (2) to develop methods for AMS education and evaluation that are applicable to non-metropolitan and multisite settings, and; (3) to develop, apply and evaluate technology in AMS, including the role of clinical decision support software and innovative educational tools such as interactive e-learning for health professional education.

Methods

This research project consisted of a series of interconnected studies that addressed AMS education and evaluation strategies at the individual, departmental, hospital and health district level. Quantitative and qualitative approaches were used to evaluate the impact of the interventions. A focus was placed on measurement of patient outcomes related to antimicrobial use, such as length of hospital stay, readmission rate and mortality. An interactive e-learning tool for health professional education on the antibiotic vancomycin was also developed and evaluated.

Results

Improvements in antimicrobial use supported by timely audit and feedback methods were demonstrated, without evident harm to patients. Those included discontinuation of the antibiotic gentamicin for prophylaxis around hip and knee replacement surgeries, a reduction in the duration of therapy for community-acquired pneumonia, and a reduction in broad spectrum antimicrobial use across multiple hospitals sites resulting from implementation of AMS. A clinical decision support system was shown to be a successful tool for supporting implementation of AMS across multiple sites. A novel web-based e-learning tool that adopted serious game design concepts was also developed for education of health professionals. Successful change to the culture of antimicrobial use from the individual to the health district level was demonstrated.

Discussion

The results suggest that educational strategies, supported by technology and antimicrobial restriction, can be effective in improving antimicrobial use in a network of hospitals with

disparate geography and resources. The application of similar techniques across different settings created economies of scale, which allowed support of smaller sites by larger, better resourced hospitals. Future research aims to demonstrate the effect of changes to antimicrobial use patterns on AMR, and to further elaborate novel educational strategies for improving antimicrobial use.

Table of contents

Certification	3
Verification	4
Acknowledgements.....	5
Publications constituting this thesis	7
Published articles	7
Articles in press.....	7
Articles under review	8
Other publications arising from this thesis	9
Presentations arising from this thesis.....	13
Abstract	15
Table of contents.....	18
List of figures.....	27
List of tables.....	29
List of key acronyms and definitions.....	31
1 General introduction	34
1.1 Preamble.....	34
1.2 Background	35
1.3 Evaluating educational strategies	36
1.4 Rural and regional hospitals	38
1.5 Use of technology to support AMS education	39
1.6 Aims	40
1.7 Structure of the thesis	42

1.8	References	48
2	Discontinuation of peri-operative gentamicin use for indwelling urinary catheter manipulation in orthopaedic surgery	55
2.1	Summary statement	55
2.2	Abstract	56
2.2.1	Background	56
2.2.2	Methods.....	56
2.2.3	Results.....	56
2.2.4	Conclusions.....	57
2.2.5	Keywords	57
2.3	Introduction	58
2.4	Methods.....	60
2.4.1	Setting	60
2.4.2	Intervention	60
2.4.3	Definitions.....	61
2.4.4	Outcomes	61
2.4.5	Data sources	61
2.4.6	Statistical analyses	62
2.4.7	Ethics.....	63
2.5	Results	63
2.6	Discussion	66
2.6.1	Conclusions.....	69
2.6.2	Author disclosure statement.....	69
2.6.3	Acknowledgements.....	70

2.7	References	70
3	Impact of an antimicrobial stewardship intervention on appropriateness of prescribing for community-acquired pneumonia in an Australian regional hospital	76
3.1	Summary statement	76
3.2	Abstract	77
3.2.1	Background	77
3.2.2	Methods.....	77
3.2.3	Results.....	77
3.2.4	Conclusions.....	78
3.2.5	Keywords	78
3.3	Introduction	79
3.4	Methods.....	81
3.4.1	Setting	81
3.4.2	Participants.....	81
3.4.3	Intervention	83
3.4.4	Outcomes	84
3.4.5	Statistical analyses	84
3.4.6	Ethics.....	84
3.5	Results	85
3.6	Discussion	89
3.6.1	Conclusions.....	91
3.6.2	Acknowledgements.....	91
3.7	References	91

4	The burden of healthcare associated <i>Clostridium difficile</i> infection in a non-metropolitan setting	95
4.1	Summary statement	95
4.2	Abstract	96
4.2.1	Objective	96
4.2.2	Methods.....	96
4.2.3	Results.....	96
4.2.4	Conclusions.....	97
4.2.5	Keywords	97
4.3	Introduction	98
4.4	Methods.....	99
4.4.1	Setting	99
4.4.2	Antimicrobial stewardship	100
4.4.3	<i>Clostridium difficile</i> laboratory testing	101
4.4.4	Effect of HCA-CDI on LOS and hospital costs.....	104
4.4.5	Antimicrobial and PPI use	105
4.4.6	Statistical analyses	105
4.4.7	Ethics.....	106
4.5	Results	106
4.6	Discussion	111
4.6.1	Conclusions.....	114
4.6.2	Acknowledgements.....	115
4.7	References	115

5	Outcomes of multisite antimicrobial stewardship program implementation with a shared clinical decision support system	120
5.1	Summary statement	120
5.2	Abstract	121
5.2.1	Objective	121
5.2.2	Methods.....	121
5.2.3	Results.....	121
5.2.4	Conclusions.....	122
5.2.5	Keywords	122
5.3	Introduction	123
5.4	Methods.....	124
5.4.1	Setting	124
5.4.2	Intervention	125
5.4.3	Outcomes	129
5.4.4	Data sources	130
5.4.5	Statistical analyses	131
5.4.6	Ethics.....	132
5.5	Results	132
5.5.1	Antimicrobial use.....	132
5.5.2	Antimicrobial costs	134
5.5.3	HCA-CDI rates	134
5.5.4	LOS	135
5.5.5	In-hospital SMR.....	136
5.6	Discussion	136

5.6.1	Conclusions.....	141
5.6.2	Acknowledgements.....	142
5.7	References	142
5.8	Tables	149
6	Design and implementation of a novel web-based e-learning tool for education of health professionals on the antibiotic vancomycin	163
6.1	Summary statement	163
6.2	Abstract	164
6.2.1	Background.....	164
6.2.2	Objectives	164
6.2.3	Methods.....	164
6.2.4	Results.....	165
6.2.5	Conclusions.....	166
6.2.6	Keywords	166
6.3	Introduction	167
6.3.1	Internet-based learning.....	167
6.3.2	Aims of this study	169
6.4	Methods.....	169
6.4.1	Setting	169
6.4.2	Web-based vancomycin knowledge survey.....	170
6.4.3	Design and implementation of the VI.....	172
6.4.4	User acceptance evaluation.....	177
6.4.5	Outcome measures	177
6.4.6	Statistical analyses	178

6.4.7	Ethics.....	179
6.5	Results	179
6.5.1	Vancomycin knowledge survey prior to release of the VI	179
6.5.2	Vancomycin Interactive	182
6.5.3	Comparison of responses between VI and web-based survey	183
6.5.4	User acceptance evaluation of the VI	184
6.6	Discussion	186
6.6.1	Principal findings	186
6.6.2	Limitations of this study	189
6.6.3	Conclusions.....	191
6.6.4	Acknowledgements.....	192
6.7	References	192
7	Evaluating the effect of a web-based e-learning tool for health professional education on clinical vancomycin use: a comparative study	197
7.1	Summary statement.....	197
7.2	Abstract	198
7.2.1	Background.....	198
7.2.2	Objectives	198
7.2.3	Methods.....	198
7.2.4	Results.....	199
7.2.5	Conclusions.....	199
7.2.6	Keywords	199
7.3	Introduction	200
7.3.1	Internet-based learning.....	200

7.3.2	Vancomycin education.....	200
7.3.3	Aims of this study	201
7.4	Methods.....	202
7.4.1	Pre-and post-intervention vancomycin knowledge survey	203
7.4.2	VI and clinical email update	204
7.4.3	Vancomycin trough plasma levels and approvals on the CDSS.....	207
7.4.4	Outcome measures	208
7.4.5	Statistical analyses	208
7.4.6	Ethics.....	209
7.5	Results	209
7.5.1	Vancomycin knowledge survey	209
7.5.2	Resources used to answer survey questions.....	210
7.5.3	Multivariate analysis of knowledge survey scores	211
7.5.4	Vancomycin TDM	212
7.5.5	Vancomycin trough plasma levels compared with vancomycin CDSS approvals	213
7.6	Discussion	214
7.6.1	Principal findings	214
7.6.2	Interpretation of results	215
7.6.3	Study limitations	216
7.6.4	Conclusions.....	219
7.6.5	Acknowledgements.....	219
7.7	References	219
8	General discussion	223

8.1	Preamble.....	223
8.2	Overview of findings.....	224
8.3	Implications.....	227
8.4	Strengths.....	228
8.5	Limitations	230
8.6	Suggestions for future research	231
8.7	Conclusions.....	232
8.8	References	234
9	Appendices.....	237
	Appendix A.....	237
	Literature search methodology	237
	Appendix B	240
	Ethics materials and data collection form reported in Chapter 2.....	240
	Appendix C	243
	Ethics materials and data collection form reported in Chapter 3.....	243
	Appendix D.....	247
	Ethics materials and data collection form reported in Chapter 4.....	247
	Appendix E	252
	Ethics materials reported in Chapter 5.....	252
	Appendix F.....	255
	Ethics materials reported in Chapter 6 and Chapter 7.	255

List of figures

Figure 2.1: Timeline of study observations and interventions.....	62
Figure 2.2: The proportion of patients receiving gentamicin for catheter insertion and removal over the 6 month pre-intervention period and during each week post-intervention. The discussion and planning period is shown in grey.	66
Figure 3.1: Study flowchart	83
Figure 4.1: Study flowchart	102
Figure 4.2: CDI exemplar feedback email to admitting medical officer	103
Figure 4.3: HCA-CDI rates for the three acute hospitals in Illawarra Shoalhaven Local Health District, Australia from December 2010 to April 2016	107
Figure 4.4: Antimicrobial use for HCA-CDI cases compared with background antimicrobial use	110
Figure 5.1: Population, clinical setting, nature and timing of interventions.....	126
Figure 5.2: Impact of the AMS intervention on antimicrobial use	133
Figure 5.3: Impact of the AMS intervention on HCA-CDI rates	135
Figure 6.1: Timeline of VI design, implementation and evaluation	170
Figure 6.2: Filming of the VI.....	174
Figure 6.3: Dramatic tension created the basis for the VI's plot	176
Figure 6.4: Example of user interface for an interactive question from the VI.....	176
Figure 7.1: Map of intervention and comparator sites	202
Figure 7.2: Pre-intervention survey request emailed to staff at intervention/ comparator sites	203

Figure 7.3: Post-intervention survey request emailed to staff at intervention/ comparator sites	204
Figure 7.4: Clinical email update sent to staff at the comparator sites	207

List of tables

Table 1.1: Research collaborators for this thesis	45
Table 2.1: Patient characteristics and pre-operative screening.....	64
Table 2.2: Gentamicin use, surgical site infections and acute kidney injury, n (%).....	65
Table 3.1: Demographic characteristics and disease severity of patients with a final diagnosis of community-acquired pneumonia	86
Table 3.2: Outcomes in patients with a final diagnosis of community-acquired pneumonia	88
Table 4.1: HCA-CDI rates before and after implementation of an ASP	108
Table 5.1: Case complexity and case mix of study hospitals for the Australian financial year 2013 – 2014.....	149
Table 5.2: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use...	150
Table 5.3: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare associated <i>Clostridium difficile</i> infection	151
Table 5.4: Length of stay and standardised mortality ratio by clinical infection group ..	152
Table 5.5a: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, by hospital.....	153
Table 5.6a: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated <i>Clostridium difficile</i> infection rates, by hospital.....	158
Table 6.1: Vancomycin knowledge survey questions.....	172
Table 6.2: Vancomycin Interactive questions.....	175
Table 6.3: Number of correct responses to web-based vancomycin knowledge survey, n (%).....	180

Table 6.4: Multivariate analysis of vancomycin knowledge survey responses (n=577) .	181
Table 6.5: Number (%) of correct answers on first attempt by nurses, doctors and pharmacists from VI data.....	183
Table 6.6: Qualitative responses (%) following participation in the VI.....	184
Table 6.7: Qualitative survey feedback on the Vancomycin Interactive	185
Table 7.1: Pre- and post-intervention median knowledge survey score, n (IQR).....	211
Table 7.2: Pre- (4 months) and post-intervention (2 months) vancomycin plasma trough levels for intervention and comparator sites, n (%)	213
Table 7.3: Proposed development and evaluation checklist for health professional e-learning tools.....	218

List of key acronyms and definitions

ACSQHC	Australian Commission on Safety and Quality in Health Care
AIHW	Australian Institute for Health and Welfare
AKI	Acute kidney injury
AMO	Attending medical officer
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
ASP	Antimicrobial stewardship program
AU\$	Australian dollar
CAP	Community-acquired pneumonia
CDI	<i>Clostridium difficile</i> infection
CDSS	(Computerised) Clinical decision support system
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CORB	Confusion, oxygen saturation, respiratory rate, blood pressure
CURB-65	Confusion, urea, respiratory rate, blood pressure, age > 65 years
CNS	Central nervous system
DDD	Defined daily dose
DRG	Diagnosis-related group
ED	Emergency Department
eMR	Electronic medical record

ESBL	Extended spectrum beta-lactamase
GDH	Glutamate dehydrogenase
HCA	Healthcare associated
HCA-CDI	Healthcare associated <i>Clostridium difficile</i> infection
HIV	Human immunodeficiency virus
IBL	Internet-based learning
ICU	Intensive Care Unit
ID	Infectious diseases
IDC	Indwelling urinary catheter
IQR	Interquartile range
ISLHD	Illawarra Shoalhaven Local Health District
IT	Information technology
ITS	Interrupted time series
IV	Intravenous
LOS	Length of hospital stay
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NAPS	National Antimicrobial Prescribing Survey
NAUSP	National Antimicrobial Utilisation Surveillance Program
NHS	National Health Service (England)
NSW	New South Wales
NWAU	National weighted activity unit
OBD	Occupied bed day
PCR	Polymerase chain reaction

PDSA	Plan-Do-Study-Act
PPI	Proton pump inhibitor
SESLHD	South Eastern Sydney Local Health District
SMART-COP	systolic blood pressure, multilobar x-ray involvement, albumin, respiratory rate, tachycardia, confusion, oxygen, pH
SMR	Standardised mortality ratio
SSI	Surgical site infection
TDM	Therapeutic drug monitoring
UOW	University of Wollongong
UTI	Urinary tract infection
VI	Vancomycin Interactive
VRE	Vancomycin-resistant <i>Enterococcus</i>
WHO	World Health Organisation

1 General introduction

1.1 Preamble

The World Health Organisation (WHO) has described antimicrobial resistance (AMR) as one of the main threats to human health in the twenty-first century (World Health Organisation, 2014). Governments around the world have recognised that an international effort is required to curb AMR, whereby overuse of antimicrobials has led to a situation where previously treatable infections can now become life-threatening. In Australia, management of infections in hospitals forms a key component of the strategy for addressing AMR (Australian Government, 2015). In 2010, the first edition of *Antimicrobial Stewardship in Australian Hospitals* was published by the Australian Commission on Safety and Quality in Health Care (ACSQHC), which offered a framework for improving the treatment and prevention of infections through more judicious use of antimicrobials (Duguid and Cruickshank, 2010).

This introductory chapter provides a brief background on strategies for improving antimicrobial use, with a focus on evaluating strategies for education at the individual, department, hospital and health district level. It identifies that there is limited published evidence for these strategies in the non-metropolitan setting where health care facilities experience geographic and resource disparities. The specific aims of the research and an outline of the thesis structure are also provided.

1.2 Background

Antimicrobial stewardship (AMS), or antibiotic stewardship, is defined as a set of strategies intended to improve the use of antimicrobials (Duguid and Cruickshank, 2010). Antimicrobial stewardship programs (ASPs) are a required component for accreditation according to ACSQHC standards, which have been introduced to drive safety and quality in public and private health care organisations in Australia (Australian Commission on Safety and Quality in Health Care, 2011). ASPs are implemented with the goals of treating and preventing infections more effectively, while curbing AMR and reducing adverse outcomes for patients (Ashiru-Oredope et al., 2012). Previously reported patient-related outcome measures used to evaluate AMS include mortality, length of hospital stay (LOS) and readmission rates (Khadem et al., 2012). Various approaches for establishing, maintaining and measuring the success of ASPs include: implementation of clinical guidelines; formulary restriction and approval systems; education on appropriate prescribing of antimicrobials; and audit with intervention and feedback to the prescriber (Dellit et al., 2007; Duguid and Cruickshank, 2010).

High rates of inappropriate antimicrobial prescribing in Australian hospitals have been described in the literature (Robertson et al., 1999; Robertson et al., 2002; Radford et al., 1999; To et al., 1999). Improving appropriateness of prescribing according to accepted antimicrobial guidelines is a key strategy for ASPs (Dellit et al., 2007). Furthermore, ASPs have been effective in reducing AMR in selected settings (Yong et al., 2010; Khadem et al., 2012). Organisms commonly targeted as part of these programs include

methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE) and multidrug resistant Gram-negative species (Khadem et al., 2012).

Improvements in the quality of antimicrobial prescribing have been associated with: improved cure rates, reduced adverse events, *Clostridium difficile* infection (CDI), reduced LOS and reduced infection-related mortality (Davey et al., 2013). Some ASPs have demonstrated reduced costs without causing harm to patients (Dellit et al., 2007; Carling et al., 2003). A common limitation of many AMS studies is their uncontrolled before-and-after design, with some studies not accounting for external factors such as changes in drug-acquisition costs and infection control practices (Vettese et al., 2013; McGowan, 2012). To compensate for the potential methodological shortcomings of pragmatic clinical research, interrupted time series (ITS) analysis, or analysis of change in trend attributable to an intervention, has been used as an effective evaluation tool (van Kasteren et al., 2005).

1.3 Evaluating educational strategies

A number of methods have been developed for improving antimicrobial prescribing. A Cochrane review of interventions to improve antimicrobial prescribing for hospital inpatients categorised interventions into three groups: persuasive (or educational), restrictive and structural (Davey et al., 2013). Examples of persuasive interventions include printed educational material, reminders, audit and feedback, and educational outreach in the form of academic detailing and recommending change. Restrictive interventions include compulsory order forms, requirement for expert approval, stock restriction (removal of antimicrobials from clinical areas), and “review and make change”

strategies. Restrictive interventions have demonstrated greater initial effects on antimicrobial use whereas educational interventions may be more durable over time. Structural interventions include computerised clinical decision support systems (CDSSs) and introduction of quality monitoring mechanisms (Davey et al., 2013). The updated Cochrane review by Davey and colleagues (2017) identifies “enabling” interventions as audit and feedback, educational outreach and reminders. Evaluation of educational interventions forms the main theoretical framework for this research, whereby education is supported by restrictive and structural interventions.

When developing educational AMS strategies, it is necessary to recognise concepts such as medical hierarchy, targeting of opinion leaders and unwillingness of prescribers to alter prescriptions started by medical colleagues (Charani et al., 2011). Study designs for improving antimicrobial use should include multiple quality improvement methods, developing an understanding of the target audience’s motivations (Charani et al., 2011; Gaynes et al., 2009; Antoine et al., 2006). It is also necessary to recognise differences in learning styles between junior and senior medical staff (Gaynes et al., 2009). Prospective audit with educational feedback is an important component of AMS education (Duguid and Cruickshank, 2010). Timely feedback allows for meaningful changes to the therapy of the individual patient, in addition to providing quality improvement data (Griffith et al., 2012).

It has been proposed that a strategy for health care quality improvement should include the following: measurement that is practical and goal-oriented; gathering baseline data on small numbers initially and checking findings; improving the delivery process while

gathering data; and following these up with graphical representation of data and measurement of key outcomes over time (Nelson et al., 1998). Emphasis on usefulness rather than perfection is readily applicable to AMS methodology as the focus should be on making measurable improvements to processes and outcomes that are relevant to patient care. Outcome measures for ASPs should include balancing measures, or unintended consequences of changes to antimicrobial use (Davey et al., 2013; Davey et al., 2017).

This research project employs a series of Plan-Do-Study-Act (PDSA) cycles as a pragmatic methodological approach to improving antimicrobial prescribing practices (National Health Service Institute for Innovation and Improvement, 2008). ITS analysis is used as a pragmatic quasi-experimental technique to evaluate the impact of AMS interventions (Fowler et al., 2007), where the immediate clinical need for change may hamper the application of more robust research methodologies.

1.4 Rural and regional hospitals

Much of the literature supporting AMS has been produced in metropolitan teaching hospitals with on-site access to infectious diseases (ID), microbiology and pharmacy expertise (Dellit et al., 2007). There is little primary evidence on ASPs in small, rural or regional hospitals. Approaches to AMS in those settings have included education, clinical review, and implementation of clinical guidelines (LaRocco, 2003). Antimicrobial restriction has typically been reported in response to infection outbreaks such as CDI (Kuntz et al., 2007; Schabas et al., 2012). Barriers to successful implementation and evaluation of ASPs in those sites include a lack of human resources for education and

research, large distances from AMS experts and microbiology laboratories, and the potential for small numbers to limit conclusions about any interventions. It is necessary for hospitals to tailor approaches to their specific needs and level of resources (Patel, 2010). Of the 1345 hospitals in Australia, 753 are public hospitals, comprising 80 principal referral hospitals, 40 large hospitals and 589 hospitals defined as medium-sized or smaller (Australian Institute of Health and Welfare, 2013). With such a large number of smaller Australian hospitals, there is a need to address the evidence gap on pragmatic approaches to improving antimicrobial use in these settings.

1.5 Use of technology to support AMS education

Use of computerised clinical decision support systems (CDSSs)

CDSSs are software tools that bring together patient-specific data and knowledge bases (Thursky, 2006). In the setting of AMS, this commonly refers to provision of evidence-based guidelines for selection and dosing of antimicrobials for a specific infection. As prescribing is a complex task that involves integrating information (often incomplete) from a variety of sources, and potential time pressure, a CDSS may be employed to reduce the cognitive effort required to prescribe (Sintchenko and Coiera, 2003). A CDSS also offers improved potential for education through provision of links to guidelines, and improved monitoring and reporting of antimicrobial use (Baysari et al., 2016).

Use of email as a communication strategy in clinical research

Given the geographic disparity of some hospital locations within the health districts studied (Australian Institute of Health and Welfare, 2016), provision of timely clinical audit feedback using face-to-face methods can be challenging. Email is described as a

tool to report research findings at an individual and department level, and to provide links to knowledge and attitude surveys. However, low response rates have been reported in the literature, with lack of time and survey burden described as the main reasons for non-response (Cunningham et al., 2015). An investigation into the utility of email as a communication method for clinical quality improvement is explored in this research project.

Novel strategies for health professional education

The use of internet-based learning (IBL), or web-based learning, for health professional education is an emerging field (Cook et al., 2008). As an educational approach, IBL can overcome some of the barriers that are experienced by traditional educational methods, such as increased clinical demands preventing face-to-face teaching (Cook et al., 2010). Web-based e-learning tools that adopt serious game concepts such as interactivity and entertainment have the potential to improve health professional education (Graafland et al., 2012). In AMS, smartphone availability may also drive novel educational approaches for health professionals (Goff, 2012). Novel IBL approaches also provide opportunities for AMS research.

1.6 Aims

This research project aims to contribute new knowledge regarding the best methods of education and evaluation to improve antimicrobial use in a multisite hospital setting, and to inform future AMS research.

The specific aims of this research are:

1. To develop and evaluate educational strategies for improving antimicrobial use in different clinical settings:
 - prevention of infection (surgical prophylaxis; Chapter 2)
 - treatment of infection (community-acquired pneumonia [CAP]; Chapter 3)
 - adverse effects of antimicrobial overuse (CDI; Chapters 4 and 5)
 - dosing, administration and therapeutic drug monitoring (TDM; vancomycin; Chapters 6 and 7)
2. To develop methods for AMS education and evaluation that are applicable to non-metropolitan and multisite settings, including:
 - use of timely audit and feedback (Chapters 2, 3 and 4)
 - appropriate evaluation of outcome measures such as mortality, LOS, duration of therapy, and health costs (Chapters 3, 4 and 5)
 - use of ITS methodology for evaluation of AMS research (Chapters 4 and 5)
3. To develop, apply and evaluate technology for improving antimicrobial use, including:
 - the role of a CDSS as a tool for implementing an ASP and supporting quality improvement initiatives (Chapters 3, 4 and 5)
 - the utility of email as a method of feedback and education for clinicians (Chapters 2, 3, 4 and 7)
 - innovative methods for health professional education such as a web-based e-learning tool (Chapters 6 and 7)

1.7 Structure of the thesis

This thesis has been prepared in the format of journal article compilation. This was considered to be the most appropriate style for the thesis content due to the common education and evaluation themes between chapters. Chapters 2 through 7 comprise six articles; five have been published or are in press, one has been submitted for editorial review. Although the articles are formatted according to the guidelines of each journal, the referencing style has been changed to Harvard style for consistency throughout the thesis, with references placed at the end of each chapter. In order to enhance the coherence of this thesis by compilation, a brief summary of each chapter is provided below.

Chapter 2 reports on an initiative to improve antimicrobial use for prevention of infections related to prosthetic hip and knee replacements. Quality improvement methodology is employed, using the combination of departmental education with timely audit and feedback to individual prescribers. Use of email to overcome communication barriers with senior doctors is described. The article was written by the candidate with co-authors Craig Boutlis, Stuart Jansen and Spiros Miyakis, and was published in the *Australian New Zealand Journal of Surgery* (Bond et al., 2016a).

Chapter 3 provides a model for improving the antimicrobial treatment of community-acquired pneumonia (CAP), one of the most common and serious infections. A similar educational framework as used in Chapter 2 is described, including the use of timely email feedback of audit results. Education for decision makers (senior medical staff) and

at the departmental level on appropriate use of antimicrobials was central to the improvement methodology. The CDSS was used as a tool to assist the data collection process. The article was written by the candidate with co-authors Craig Boutlis, Wilf Yeo and Spiros Miyakis, and was published as a brief communication in *Internal Medicine Journal* in 2017 (in press) (Bond et al., 2017a).

Chapter 4 describes a research project on an adverse effect from inappropriate antimicrobial use, CDI. A multisite methodology for reducing inappropriate use of causative antimicrobials is described, including use of timely email feedback to senior clinicians and a CDSS for monitoring of antimicrobial use. The chapter also reports hospital costs and LOS as key AMS outcome measures. The article was written by the candidate with co-authors Craig Boutlis, Wilf Yeo, William Pratt, Megan Orr, and Spiros Miyakis. It was published in the *Journal of Hospital Infection* in 2016 (Epub ahead of print) (Bond et al., 2016b).

Chapter 5 provides an overview of implementation and evaluation of an ASP across multiple hospital sites, with antimicrobial use, CDI, antimicrobial costs, LOS and mortality as indicators of improvement. Hospitals from two health districts and a specialist children's hospital are included in the report. A centrally deployed CDSS and various educational strategies are explored as tools for implementing and evaluating a multisite ASP across hospitals with varying resources, including those in regional and rural areas. The article was written by the candidate with co-authors Adriana Chubaty, Suman Adhikari, Spiros Miyakis, Craig Boutlis, Wilf Yeo, Marijka Batterham, Cara Dickson, Brendan McMullan, Mona Mostaghim, Samantha Li-Yan Hui, Kate Clezy, and

Pamela Konecny. The article was published in the *Journal of Antimicrobial Chemotherapy* in 2017 (in press) (Bond et al., 2017b).

Chapter 6 reports on the design and implementation of a novel web-based e-learning tool for health professional education on antimicrobial use. The specific antimicrobial tested is vancomycin, used for treatment of serious infections caused by MRSA. The Vancomycin Interactive (VI) is proposed as a useful approach where the multiple hospitals within a health district are spread across a large geographic area, thereby addressing a barrier to ongoing education. Through its hosting on an open website, the game can also be easily used in smaller rural and regional hospitals. Qualitative survey methodology is employed to report on knowledge and attitudes related to the intervention. The article was written by the candidate with co-authors Shelley Crowther, Suman Adhikari, Adriana Chubaty, Ping Yu, Jay Borchard, Craig Boutlis, Wilf Yeo, and Spiros Miyakis. The article was published in *Journal of Medical Internet Research* in 2017 (in press) (Bond et al., 2017c).

Chapter 7 further explores the use of the VI for health professional education, through comparison with a standard email intervention. As in Chapters 3, 4 and 5, the CDSS is used to support evaluation of the initiative. Further research on evaluation of the e-learning tool is also described. The article was written by the candidate with co-authors Shelley Crowther, Suman Adhikari, Adriana Chubaty, Ping Yu, Jay Borchard, Craig Boutlis, Wilf Yeo, and Spiros Miyakis. The article was under review in *Journal of Medical Internet Research: Medical Education* in March 2017.

Chapter 8 provides a summary of project findings followed by a discussion on the implications, strengths and limitations of the research. Suggestions for future research and thesis conclusions are also presented.

A full list of collaborators, their roles and areas of expertise are provided in Table 1.1 below.

Table 1.1: Research collaborators for this thesis

Research collaborator	Site	Position	Areas of expertise
Wilf Yeo	Wollongong Hospital; UOW	Professor of Medicine; thesis supervisor	Research planning, data analysis, critical review
Craig Boutlis	Wollongong Hospital; UOW	ID physician; thesis supervisor	AMS, data collection and analysis, scientific writing
Spiros Miyakis	Wollongong Hospital; UOW	ID physician; Associate Professor of Medicine; thesis supervisor	AMS, research planning, manuscript review and submission
Stuart Jansen	Wollongong Hospital	Wollongong Hospital Orthopaedic surgeon	Project implementation, manuscript review

William Pratt	Shoalhaven Hospitals; UOW	General/ ID physician; health district lead for AMS	AMS, project design and implementation, manuscript review
Megan Orr	Shoalhaven Hospitals	AMS pharmacist	AMS, data collection, manuscript review
Adriana Chubaty	Prince of Wales Hospital	AMS pharmacist	AMS, project design, data collection and analysis, manuscript review
Suman Adhikari	St George Hospital	AMS pharmacist	AMS, data collection and review, project implementation; critical review
Marijka Batterham	UOW	Associate Professor of applied statistics	Project design, statistics
Cara Dickson	St George Hospital	Performance analyst	Data collection and analysis
Brendan McMullan	Sydney Children's Hospital	Paediatric ID physician	AMS, project implementation, manuscript review
Mona Mostaghim	Sydney Children's Hospital	Paediatric AMS pharmacist	AMS, project implementation, manuscript review

Samantha Li-Yan Hui	Prince of Wales Hospital	CDSS administrator pharmacist	AMS, CDSS support, coordination of data collection
Kate Clezy	Prince of Wales Hospital	ID physician	AMS, project design and implementation, manuscript review
Pamela Konecny	St George Hospital	ID physician	AMS, literature review, manuscript review
Shelley Crowther	Wollongong Hospital	District educator pharmacist	Survey design, project design and implementation, manuscript review
Ping Yu	UOW	Associate Professor of Health Informatics	Survey design, study design, manuscript review
Jay Borchard	Wollongong Hospital	Clinical researcher	Statistical analysis, manuscript review

UOW, University of Wollongong

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2 Discontinuation of peri-operative gentamicin use for indwelling urinary catheter manipulation in orthopaedic surgery

Article published in *ANZ Journal of Surgery* (2016).

Bond SE, Boutlis CS, Jansen SG, and Miyakis S (2016). 'Discontinuation of peri-operative gentamicin use for indwelling urinary catheter manipulation in orthopaedic surgery', *ANZ Journal of Surgery*, doi: 10.1111/ans.13642 (Epub ahead of print).

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2.1 Summary statement

This chapter offers a model for improving antimicrobial use related to prevention of infection around orthopaedic surgery. Educational themes explored as part of this project include: use of timely audit and feedback, departmental education with subsequent reporting of post-intervention results by email, and tailoring of an educational strategy to senior surgical staff through the use of peer education. Those themes are further explored in Chapters 3 and 4.

2.2 Abstract

2.2.1 Background

Gentamicin has historically been used prior to insertion and removal of indwelling urinary catheters (IDCs) around elective joint replacement surgery to prevent infection; however, this indication is not recognised in the Australian *Therapeutic Guidelines: Antibiotic* and the paradigm for safe use of gentamicin has shifted.

2.2.2 Methods

The AMS team of a 500 bed tertiary regional hospital performed a retrospective clinical study of gentamicin IDC prophylaxis around total hip and knee arthroplasties. Results were presented to the orthopaedic surgeons. A literature review identified no guidelines to support gentamicin prophylaxis and only a very low risk of bacteraemia associated with IDC insertion/removal in patients with established bacteriuria. Consensus was reached with the surgeons to discontinue this practice. Subsequent prospective data collection was commenced to determine effectiveness, with weekly feedback to the Department Head of Orthopaedics.

2.2.3 Results

Data from 137 operations pre-intervention (6 months) were compared with 205 operations post-intervention (12 months). The median patient age was 72 years in both groups. Following the intervention, reductions in gentamicin use were demonstrated for IDC insertion (59/137 [42%] to 4/205 [2%], $p<0.01$) and removal (39/137 [28%] to 6/205

[6%], $p < 0.01$). No gentamicin use was observed during the final 40 weeks of the post-intervention period. There were no significant differences between the groups for pre-operative bacteriuria, surgical site infections (SSIs) or acute kidney injury (AKI).

2.2.4 Conclusions

A collaborative approach using quality improvement methodology can lead to an evidence based reappraisal of established practice. Regular rolling audits and timely feedback were useful in sustaining change.

2.2.5 Keywords

Antibiotic prophylaxis, gentamicin, arthroplasty, in-dwelling catheters, surgical site infection

2.3 Introduction

Urinary catheterisation is common during the peri-operative period and is associated with increased risk of bacteriuria and symptomatic urinary tract infection (UTI) (Marschall et al., 2013). In contrast, bacteraemia from IDC manipulation is rare, even when indwelling times are longer (Polastri et al., 1990; Jewes et al., 1988; Bregenzer et al., 1997). A causal link has not been established between peri-operative asymptomatic bacteriuria, bacteraemia and subsequent haematogenous seeding of the prosthetic joint (Sousa et al., 2014). Studies have reported either no effect (Britt et al., 1977) or modest reduction (Jaffe et al., 1985; Mountokalakis et al., 1985; Romanelli et al., 1990; Esposito et al., 2006; Pfefferkorn et al., 2009; Petronella et al., 2012; van der Wall et al., 1992) in rates of bacteriuria and UTIs from antibiotic prophylaxis around short term IDC use. Several limitations applied: small sample sizes, none examined aminoglycosides, and the effect on antibiotic resistance was not routinely examined. In addition, the studies were not performed in the setting of orthopaedic surgery, and did not examine the impact on SSIs.

Gentamicin is an aminoglycoside antibiotic administered intravenously for the treatment of Gram-negative infections (Leong et al., 2006). Gentamicin is also recommended as prophylaxis for surgery with high risk of Gram-negative infections, such as urological procedures (Antibiotic Expert Group, 2010). Due to concerns over side effects such as ototoxicity and nephrotoxicity, even after a single dose (Ahmed et al., 2012; Coroners Court of Victoria, 2012), there has been a shift in the paradigm of safe gentamicin use (Australian Commission on Safety and Quality in Health Care, 2015). Two recent studies examining the combination of gentamicin with a beta-lactam antibiotic for orthopaedic

surgical prophylaxis gave conflicting results on the risk of AKI (Bell et al., 2014; Craig et al., 2012). Both highlighted the presence of additional potentially nephrotoxic factors (e.g. older age, fractures, volume loss, anti-hypertensive medications and analgesics).

The Australian *Therapeutic Guidelines: Antibiotic* (Antibiotic Expert Group, 2010) recommend against the routine use of gentamicin in the setting of peri-operative IDC insertion and removal and this recommendation has not changed in the latest update (Antibiotic Expert Groups, 2014). Despite guideline recommendations, gentamicin had been used as peri-operative prophylaxis in around one third of orthopaedic patients in our hospital. Some surgeons were initially reluctant to abandon gentamicin use, due to concerns about a potential increase in SSI rates and medico-legal considerations related to not following an established historical practice.

Education and quality improvement are fundamental aspects of AMS in hospitals (Davey et al., 2013). Recent evidence suggests that feedback as a component of the change management process is more effective when it is: frequently presented; delivered by a peer; and aims to decrease a specific behaviour (Ivers et al., 2014). Our study analysed the effect of education with rapid-cycle audit and feedback, a method that may be effective where clinicians have previously agreed to review their practice (Ivers et al., 2012). The importance of engaging with stable staff groups such as consultant surgeons and anaesthetists became evident. We assessed the impact of a group of interventions that aimed to reduce prophylactic gentamicin use during IDC insertion and removal in orthopaedic surgery, without increasing SSI rates. This quality improvement initiative

could constitute an effective model for management of change in the setting of limited background data.

2.4 Methods

2.4.1 Setting

We initially performed a retrospective clinical study at Wollongong Hospital, a regional 500 bed university teaching hospital in New South Wales (NSW), Australia. The AMS team (pharmacist and ID physician) identified the use of gentamicin as prophylaxis for IDC insertion and removal during a routine retrospective audit of systemic antibiotic prophylaxis around total hip and knee arthroplasties and revisions. IDC use was routine in this setting. The decision to administer gentamicin and its dose were at the discretion of the surgeon and there was not a departmental policy.

2.4.2 Intervention

This study employed PDSA quality improvement methodology (National Health Service Institute for Innovation and Improvement, 2008). The timeline of observations and interventions is shown in Figure 2.1. The guideline recommendations for routine surgical prophylaxis were the same for both the pre- and post-intervention groups (cephazolin routinely, with or without vancomycin following risk assessment for MRSA) (Antibiotic Expert Group, 2010). Notably, there was discussion with the surgeons and anaesthetists around guideline-concordant prescribing during the time interval (March 2012 to January 2013) from the presentation of initial findings until the main intervention point.

Discussion also occurred at the AMS committee meetings (which included a surgeon representative) during this time.

2.4.3 Definitions

SSIs were defined according to standard definitions (Australian Council on Healthcare Standards, 2014) and reported by mandate to the NSW Ministry of Health. AKI was defined by the Kidney Disease Improving Global Outcomes criteria as a >50% rise above baseline serum creatinine (Kidney Disease Improving Global Outcomes, 2012).

Assessment for vestibular toxicity was available, as dictated by patient symptoms.

2.4.4 Outcomes

The effect of the intervention was assessed using the following measures: prevalence of gentamicin use for insertion and removal of IDCs; comparative SSI rates; proportion of patients with AKI 48-72 hours post-operation.

2.4.5 Data sources

A retrospective dataset of total hip and total knee arthroplasties was obtained from medical records for the period 1 January to 30 June 2011. Gentamicin use was assessed from anaesthetic and medication charts, and serum creatinine measurements were retrieved from the electronic medical record (eMR; Cerner Powerchart™). Arthroplasty data were collected prospectively during the post-intervention period (February 2013 to February 2014) from the eMR and ward list. The infection control service provided SSI rates.

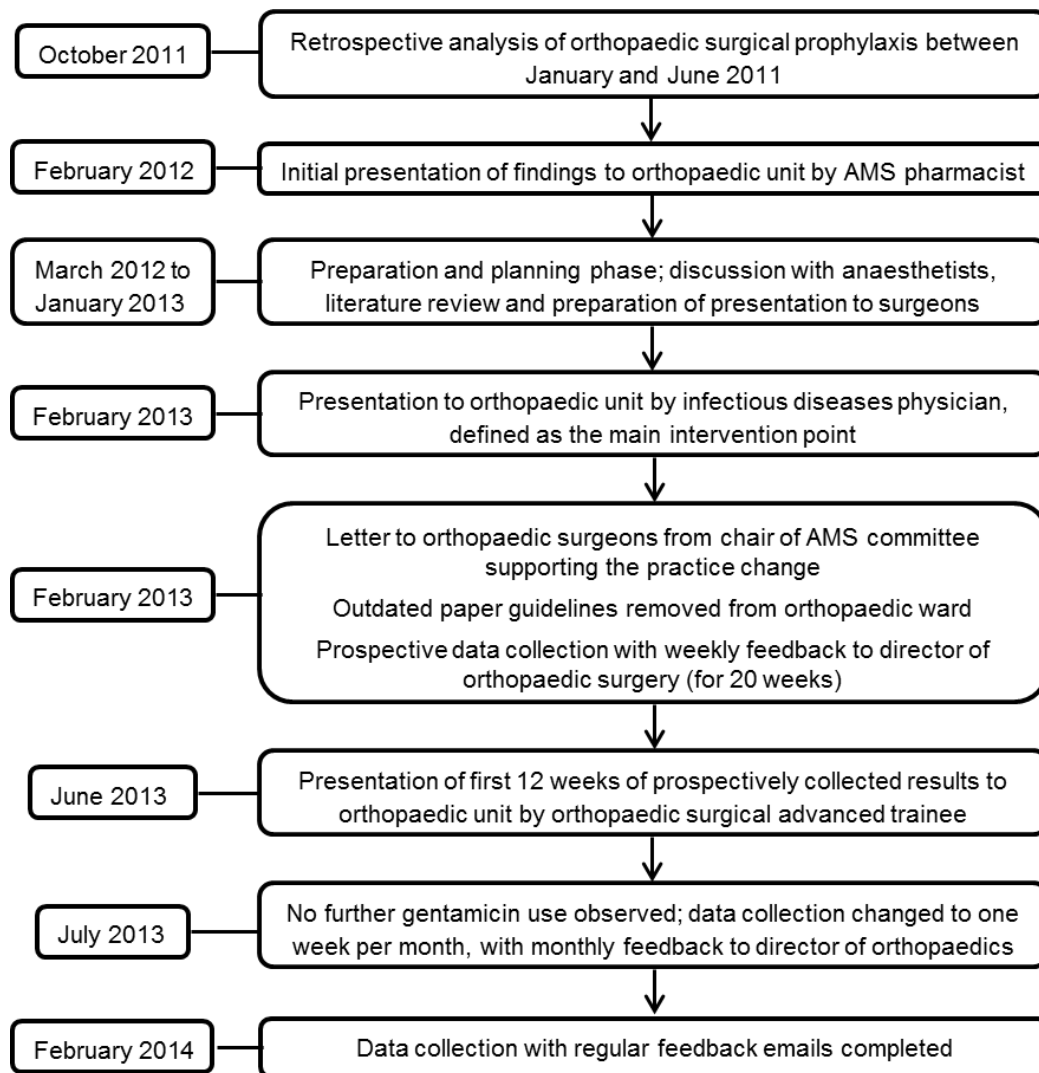


Figure 2.1: Timeline of study observations and interventions

2.4.6 Statistical analyses

Statistical analyses were performed using Stata statistical software: Release 14 (Statacorp LP, College Station, TX, USA). Chi-square and Fisher's exact tests were used as appropriate. A Shapiro-Wilk test was used to check for normal distribution, and Mann-Whitney U-test was used for continuous variables. Statistical significance was accepted as $p < 0.05$.

2.4.7 Ethics

This study was approved by the University of Wollongong (UOW) and Illawarra Shoalhaven Local Health District (ISLHD) Human Research Ethics Committee: HE11/103 (Appendix B).

2.5 Results

Data from 137 operations pre-intervention (6 months, retrospective) were compared with 205 operations post-intervention (12 months, prospective; Table 2.1). Patient age and weight were similar in both groups; however, there were marginally more males in the post-intervention sample (31% vs. 42%, $p=0.048$). There were more positive pre-operative MRSA screening cultures in the pre-intervention group (3% vs. 0.5%, $p=0.047$). No differences were observed in the number of positive pre-operative urine samples (Table 2.1). Gentamicin doses ranged from 80mg to 240mg.

A significant reduction in gentamicin use was demonstrated post-intervention (Table 2.2). From week 12 of the post-intervention period (Figure 2.2), no further doses of gentamicin were administered for IDC manipulation.

No significant differences were found between the numbers of superficial hip, deep hip, superficial knee, or deep knee infections (Table 2.2). There were no significant changes in the rates of AKI (Table 2.2), and no reports of vestibular toxicity following gentamicin use.

Table 2.1: Patient characteristics and pre-operative screening

	Pre-intervention	Post-intervention	p value
Median age, yrs (range)	72 (40-91)	72 (35-87)	0.79
Male, <i>n</i> (%)	43 (31)	86 (42)	0.048
Median weight[†], kg (range)	82 (40-142)	82 (44-143)	0.79
Cephazolin as skin prophylaxis[‡], <i>n</i> (%)	116/137 (87)	188/205 (92)	0.13
Hip arthroplasty[§], <i>n</i> (%)	58/137 (42)	70/205 (34)	0.13
MRSA screening swab positive	4/122 (3)	1/204 (0.5)	0.047
Pathogen isolated in pre-operative urine sample, <i>n</i> (%)	25/123 (20)	28/198 (14)	0.15
Pre-op positive urines treated with antibiotics, <i>n</i> (%)	11/25 (44)	8/28 (29)	0.24

[†]Data available from 133 patients pre-intervention; 202 post-intervention; [‡]Data available from 134 patients pre-intervention, 205 post-intervention; [§]Includes revisions; ^{||}Includes mixed and single pathogen growth.

The remainder of the urine samples were reported as “no growth” or “no significant growth”.

Table 2.2: Gentamicin use, surgical site infections and acute kidney injury, n (%)

	Pre- intervention (6 months) n = 137	Discussion and planning period (20 months) n = 605	Post-intervention (12 months) n = 205	p value
Gentamicin for IDC insertion	59 (42)	N/A	4 (2)	<0.01
Gentamicin for IDC removal[†]	39 (28)	N/A	6 (3)	<0.01
Surgical site infections, deep	0 (0)	7 (1.2)	1 (0.5)	0.59
Surgical site infections, superficial	1 (0.7)	3 (0.5)	0 (0)	0.45
Post-operative acute kidney injury[‡]	2 (2)	N/A	1 (1)	0.35

[†]Data available from 137 patients pre-intervention, 204 patients post-intervention [‡]defined as >50% rise in baseline serum creatinine

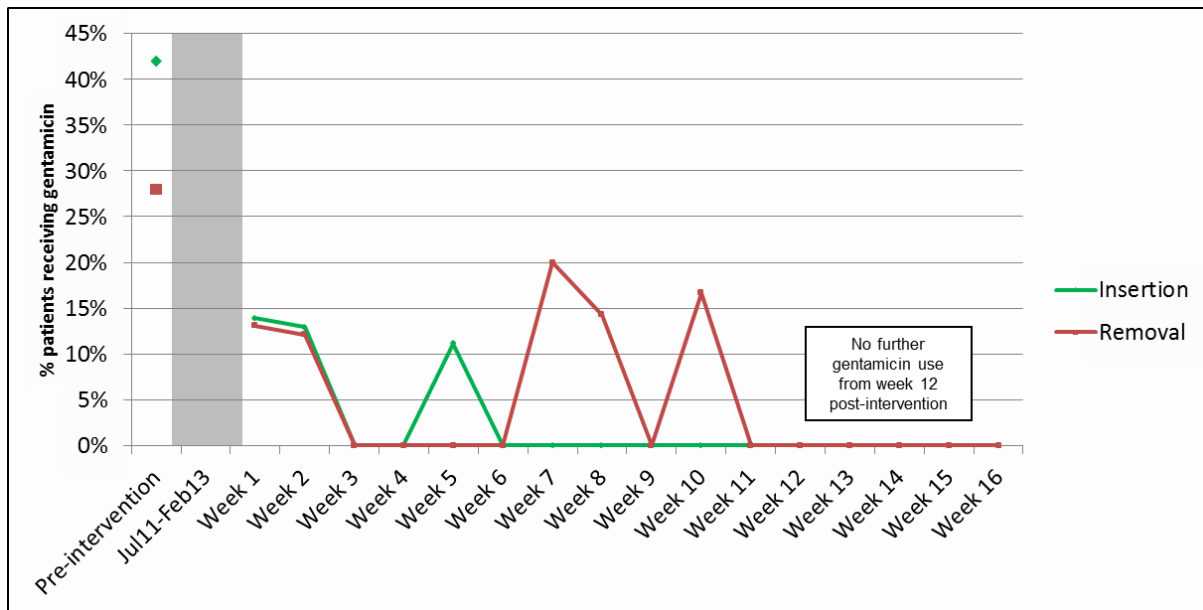


Figure 2.2: The proportion of patients receiving gentamicin for catheter insertion and removal over the 6 month pre-intervention period and during each week post-intervention. The discussion and planning period is shown in grey.

2.6 Discussion

Our study showed that a combined intervention of education and discussion with audit and timely feedback was effective in withdrawing the practice of prophylactic gentamicin for IDC insertion and removal in orthopaedic surgery. No significant changes were observed in the rates of SSI or AKI, although the study was not powered adequately to detect those. Most importantly, this study offers a model for a sustained quality improvement initiative in the setting of limited background data and contributes to emerging evidence on the beneficial role of AMS in improving antibiotic use.

The majority of infections in orthopaedic surgery are caused by Gram-positive skin flora, for which cephazolin and vancomycin (where appropriate) provide adequate prophylaxis (Antibiotic Expert Group, 2010). The potential risks and lack of clinical benefit from gentamicin in this setting formed the basis of our intervention. Rates of gentamicin use were reducing during the planning and discussion period, highlighting that the ongoing interaction resulted in gradual practice change. This was consolidated to a withdrawal of gentamicin prescribing in the study sample. The importance of directly addressing medico-legal concerns and providing written support for practice change was also recognised.

To our knowledge, this is the first study that has examined the impact of a change to IDC prophylaxis on clinical outcomes for orthopaedic surgery patients. A Cochrane review of antibiotic prophylaxis for short term IDC bladder drainage in adults showed that the primary outcome of bacteriuria was lower in the prophylaxis group (Lusardi et al., 2013). There is no evidence linking insertion and/or removal of an IDC with Gram-negative bacteraemia and seeding of a newly implanted prosthesis. Although a recent study has demonstrated that asymptomatic bacteriuria was an independent risk factor for prosthetic joint infection, preoperative antibiotic treatment did not show any benefit and infecting organisms were frequently different to those isolated prior to surgery (Sousa et al., 2014). Studies reporting bacteraemia from IDCs in the setting of chronic catheterisation reported low rates of established infection (Polastri et al., 1990; Jewes et al., 1988; Bregenzer et al., 1997).

There were no deep SSIs during the pre-intervention period and only one (0.5%) post-intervention. During the intervening period the SSI rate was low at 1.1%, comparable with existing literature (Kurtz et al., 2008; Havelin et al., 2000). These differences were not statistically significant. Studies powered to detect changes in rare outcomes such as SSI rates typically require larger sample sizes (Havelin et al., 2000; Kurtz et al., 2008; Al-Mulhim et al., 2014).

The rate of peri-operative AKI in our study was 1-2%. Rates have been previously reported at 11% for orthopaedic surgeries with routine gentamicin prophylaxis, but with different gentamicin doses (Bell et al., 2014). The lower rate in our study may be due to the lower doses of gentamicin for IDC prophylaxis than for routine skin prophylaxis.

A focus on immediate clinical outcomes (gentamicin toxicity) rather than parameters that appear later (antibiotic resistance) may have stronger influence on prescribing behaviour (Broom et al., 2014). Other strategies to reduce the risk of IDC-related UTI in the peri-operative setting include: intermittent or no catheterisation, early mobilisation (that shortens the period when the IDC needs to remain in place), training for insertion techniques, good IDC care and consideration of IDC materials (Gould et al., 2010). Male patients receiving epidural anaesthesia may be at greater risk of urinary retention in the setting of orthopaedic surgery (Griesdale et al., 2011; Hollman et al., 2015; Lingaraj et al., 2007).

There were several limitations to our study. These included confounding factors that may influence SSI rates (skin preparation, surgical technique, patient comorbidities) and the

significantly larger proportion of male patients in the post-intervention sample (probably resulting from variation in data collection methods). The study was not powered to detect changes in SSI rates and those were not followed up long term, meaning that late deep infections may have been missed. The indication for gentamicin use was not routinely documented on the anaesthetic records and drug charts. The study did not follow the prescribing habits of individual surgeons, so some of the change in gentamicin use may have been due to changes in staff. There were; however, minimal staff changes at a senior level during the study period. We believe that interpersonal interactions, the prevailing local culture of quality improvement and strong leadership of the units involved have contributed to the successful outcomes of this study. Those features were furthermore strengthened during the interactive audit and feedback process; generalisability to other settings needs to be tested. Audiometry was not available on site to test for gentamicin toxicity. Although we used a methodology common in pragmatic AMS research, introduction of bias may be inherent, outside a randomised controlled environment.

2.6.1 Conclusions

We have shown that a group of robust multi-disciplinary AMS interventions effected durable practice change without obvious evidence of harm. Further studies are required to demonstrate validity in other settings, as well as the impact of gentamicin prophylaxis on renal function in other types of surgery.

2.6.2 Author disclosure statement

SB, CB, SJ – none to declare

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2.6.3 Acknowledgements

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3 Impact of an antimicrobial stewardship intervention on appropriateness of prescribing for community-acquired pneumonia in an Australian regional hospital

Article published in *Internal Medicine Journal* (2017).

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3.1 Summary statement

This chapter addresses treatment of a common infection, CAP, using an educational strategy with common links to Chapters 2 and 4. Email was used as a method for providing clinical feedback and education to individual prescribers, along with combined educational interventions at the departmental level. As CAP treatment traverses the emergency department and numerous medical specialties, a hospital-wide approach was also required. Monitoring of antimicrobial prescribing was supported by a CDSS, which when combined with email feedback has applicability to multiple sites within the rural and regional health district. The multisite and rural/regional themes are further explored in Chapters 4, 5, 6 and 7.

3.2 Abstract

3.2.1 Background

CAP is the second commonest indication for antibiotic use in Australian hospitals and is therefore a frequent target for AMS interventions. The recommended duration of combined intravenous and oral empiric therapy for CAP in the Australian *Therapeutic Guidelines* (2014) is seven days. The aim of this study was to improve appropriateness of antibiotic prescribing for CAP.

3.2.2 Methods

We performed a single-centre prospective study in a regional referral hospital comparing management of adult inpatients with presumed CAP before and after an AMS intervention (pre-intervention 1 June to 30 November 2013; post-intervention 1 June to 30 November 2014). Post-intervention, individual case feedback was emailed to the attending medical officer (AMO). The primary outcome measure was duration of antibiotic therapy. Secondary outcome measures included appropriateness of therapy, LOS, 30 day readmission rate and in-hospital mortality.

3.2.3 Results

Post-intervention, median duration of therapy decreased from 11 days (n=34) to 9 days (n=79; p=0.04). The number of patients with non-severe CAP receiving the third generation cephalosporin, ceftriaxone (indicated for severe CAP) decreased from 74%

(14/19) to 45% (18/40; $p=0.04$). There were no significant differences in LOS, 30 day readmission rate or in-hospital mortality.

3.2.4 Conclusions

Our AMS intervention was successful in reducing duration of therapy and unnecessary exposure to ceftriaxone. The use of timely audit and feedback can foster improvement. As CAP therapy is responsible for a large proportion of antibiotic use in Australian hospitals, interventions are recommended to address initial choice and duration of therapy.

3.2.5 Keywords

Community-acquired pneumonia, antibiotics, duration of therapy, antimicrobial stewardship

3.3 Introduction

CAP causes significant morbidity and mortality (Maxwell et al., 2005; Postma et al., 2015) and is the second commonest indication for antibiotic prescribing in Australian hospitals, following surgical prophylaxis (Australian Commission on Safety and Quality in Health Care, 2015). Ceftriaxone (a third generation cephalosporin) plus azithromycin (a macrolide) is recommended as first-line treatment of severe CAP in non-tropical regions of Australia (Antibiotic Expert Group, 2010; Antibiotic Expert Groups, 2014), whereas benzylpenicillin plus doxycycline is recommended for moderate-severity CAP. These recommendations are based on susceptibility data for *Streptococcus pneumoniae*, the commonest causative pathogen of CAP in Australia (Charles et al., 2008), which is almost uniformly susceptible to benzylpenicillin for non-central nervous system (CNS) isolates (Newton, 2013).

Prescribing for CAP is a common target for hospital-based ASPs, due to the potential for overuse of the combination of ceftriaxone plus azithromycin for treatment of non-severe disease (Australian Commission on Safety and Quality in Health Care, 2011; Antibiotic Expert Group, 2010; Maxwell et al., 2005). Unnecessary use of those antibiotics may be associated with increased cost; the emergence of resistant pathogens such as MRSA (Paterson, 2004), extended spectrum beta-lactamase (ESBL) producing enterobacteriaceae (Paterson, 2004), and *Streptococcus pneumoniae* (Musher and Thorner, 2014); as well as CDI (Paterson, 2004).

The requirement to rapidly identify and treat sepsis in emergency departments (EDs) (Clinical Excellence Commission, 2015; Burrell et al., 2016) may drive use of broad spectrum antibiotics for initial treatment of CAP. Initial antibiotic prescribing in EDs is often continued on the wards, possibly due to a culture of non-interference among medical staff (Charani et al., 2013). Clinicians may also perceive that development of AMR is a low priority and a distant consequence of prescribing (McCullough et al., 2015).

A number of studies have demonstrated no difference in outcomes for patients with mild to moderate CAP treated with up to seven days of total antibiotic therapy compared with prolonged courses of greater than seven days (Athanassa et al., 2008; Choudhury et al., 2011; Li et al., 2007). Avdic *et al* (2012) reported a reduction of three days in median duration of CAP therapy using education and direct oral feedback to treating teams at a large metropolitan hospital. A reduction in time between measurement and feedback, and a high level of stakeholder buy-in (such as from senior medical staff) may result in better audit outcomes (Ivers et al., 2012).

We evaluated whether an intervention involving education with timely audit and emailed feedback would lead to a more appropriate duration of antibiotic therapy and a reduction in the number of patients with non-severe CAP receiving a ceftriaxone-based regimen.

3.4 Methods

3.4.1 Setting

We performed a prospective pre- and post-intervention study of patients presenting to the ED of Wollongong Hospital, a 550-bed regional tertiary referral hospital in NSW, Australia. Treatment of adult (≥ 18 years) patients with a final diagnosis of CAP was compared between pre-intervention and post-intervention cohorts (1 June - 30 November 2013 vs. 1 June - 30 November 2014).

3.4.2 Participants

Firstnet® ED software (Cerner, Kansas City, MO, USA) was viewed prospectively for admissions containing any of the following keywords in the “diagnosis” column: pneumonia; lower respiratory tract infection; chest infection. Patients in whom pneumonia was suspected were also screened where an AMO consult was requested from respiratory, general or geriatric medicine. Patients who received initial antibiotics directed at CAP were initially screened, with a final diagnosis of CAP on the discharge summary being required for study inclusion. Exclusion criteria were as follows: < 18 years of age; immunosuppressed (i.e., concurrent chemo- or immunosuppressant therapy or human immunodeficiency virus [HIV] positive); cystic fibrosis; bronchiectasis; empyema; exacerbation of chronic obstructive pulmonary disease (COPD) or asthma if not involving pneumonia; suspected or confirmed tuberculosis; aspiration or hospital-acquired pneumonia; readmitted to hospital within 14 days; transferred from another hospital. Duration of antibiotic therapy was determined from the medication charts and pharmacy

dispensing data. The remaining course of oral antibiotics was supplied to the patient on discharge.

A reference SMART-COP severity score was calculated for each patient by the AMS pharmacist to assess compliance with national antibiotic guidelines (Antibiotic Expert Group, 2010). The SMART-COP score and occasionally the CORB and CURB-65 severity scores were used by prescribers. Regimens suggested in the antibiotic guidelines broadly aligned with the mild, moderate and severe categories of CAP identified by the severity scores. Guideline compliance was recorded as: “complete” if, after accounting for allergy, all drugs matched the treatment of CAP according to SMART-COP score; “partial” if some of the drugs given matched the score; and “not at all” if none of the antibiotics matched. Ongoing monitoring of broad spectrum antimicrobial use on AMS rounds was facilitated by a CDSS, Guidance MS® (Guidance Group, 2013).

In the pre-intervention group, 42 patients were initially screened for inclusion. The use of a patient admissions report (i.PM, CSC, Wilmington, DE, USA) during the post-intervention phase, resulted in a greater number of patients included (n=99). The same screening definitions applied in both groups. Data analysis was performed on those patients with a final diagnosis of CAP on discharge summary. A CAP diagnosis was made in 34/42 (81%) assessable patients pre-intervention and 79/99 (80%) post-intervention (Figure 3.1).

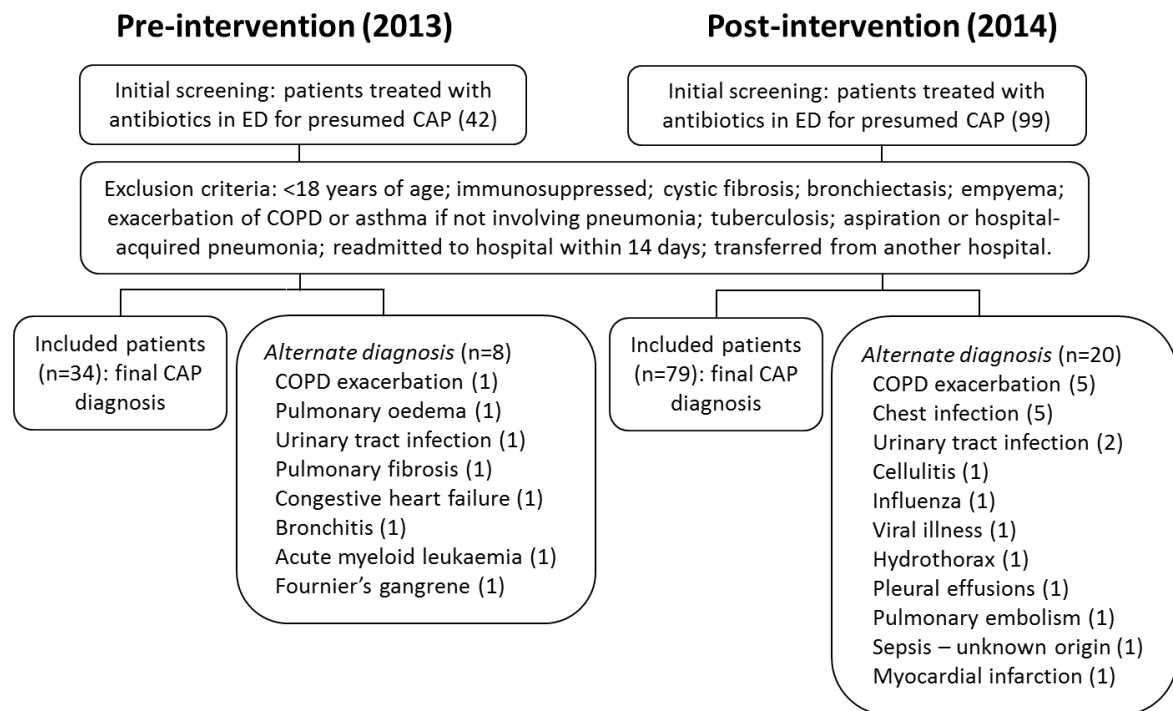


Figure 3.1: Study flowchart

3.4.3 Intervention

Pre-intervention results were presented to emergency, respiratory and general medicine, infectious diseases, pharmacy, and nursing meetings (April - May 2014). Education points included: use of severity scores; initial choice of antibiotics; change of antibiotic regimen; duration of intravenous (IV) and total therapy; and *Streptococcus pneumoniae* antibiograms. During the post-intervention phase a summary of each case was emailed by the AMS pharmacist to the AMO and junior staff, typically within two weeks of discharge. Initial antibiotic choice, subsequent treatment and duration of therapy were described in the email. The response rate of AMOs was assessed and responses were grouped as follows: (1) containing clinical feedback, (2) basic acknowledgement, or (3)

defensive. The time to collect data and send the email was approximately 30 minutes per patient. This was incorporated into the existing role of the AMS pharmacist.

3.4.4 Outcomes

The primary outcome measure was total duration of combined IV and oral antibiotic therapy. Secondary outcomes included proportion of non-severe CAP patients receiving a ceftriaxone-based regimen, documentation of severity scores; appropriateness of antibiotic therapy according to severity score; LOS; 30 day readmission rate; and in-hospital mortality.

3.4.5 Statistical analyses

Statistical analyses were performed using Stata® statistical software (Release 14, Statacorp LP, College Station, TX, USA). A chi-square test was used to compare proportions (Fisher's exact test was used when an expected cell value was less than 5), and Wilcoxon rank-sum test for comparison of continuous variables involving duration of antibiotic therapy and duration of IV therapy. All statistical tests were two tailed, differences were considered significant at $p < 0.05$.

3.4.6 Ethics

Ethics approval was granted by our institutional Human Research and Ethics Committee, approval number HE11/377 (Appendix B).

3.5 Results

Demographic characteristics were similar between the two groups (Table 3.1). Parameters for calculation of a SMART-COP score were available in 97/113 (86%) cases with a final diagnosis of pneumonia. There were no significant differences between the proportion of patients with mild, moderate and severe CAP according to SMART-COP score, and a similar number of patients received antibiotics prior to admission in both cohorts.

Respiratory medicine and general medicine accounted for 101/113 (89%) cases. Penicillin allergy was slightly more common in the pre-intervention group ($p=0.11$).

There were no significant differences in the proportion of microbiology investigations between the two cohorts. *Streptococcus pneumoniae* was the commonest organism identified in both groups.

Table 3.1: Demographic characteristics and disease severity of patients with a final diagnosis of community-acquired pneumonia

Characteristic	Pre- intervention (2013; n=34)	Post- intervention (2014; n=79)	p value
Male, n (%)	16 (47)	48(61)	0.18
Age, median (range), yrs	83 (20-93)	78 (18-95)	0.08
Penicillin allergy, n (%)	9(26)	11(14)	0.11
Antibiotics prior to ED, n (%)	9(26)	27(34)	0.42
SMART-COP 0-2 (mild), n (%)	11(32)	27(34)	0.85
SMART-COP 3-4 (moderate), n (%)	13(38)	29(37)	0.88
SMART-COP 5-11 (severe), n (%)	10(29)	23(29)	0.98

Abbreviations: ED, emergency department; SMART-COP, reference clinical severity score

The median duration of antibiotic therapy decreased from 11 days pre-intervention to 9 days post-intervention ($p=0.04$; Table 3.2). The median duration of directed therapy in patients with a positive microbiological test was 11 days pre-intervention and 10 days post-intervention. The proportion of patients with non-severe CAP treated with ceftriaxone-based therapy (with penicillin allergy cases excluded) decreased from 14/19 (74%) patients pre-intervention to 18/40 (45%) post-intervention ($p=0.04$). Among those patients, ceftriaxone was continued beyond 48 hours in only 2/14 cases pre-intervention and in 3/18 cases post-intervention; in all other cases ceftriaxone was either deescalated to oral therapy or ceased (data not shown). In the pre-intervention period, therapy was escalated in 1/34 (3%) cases following the results of the laboratory investigations,

compared to 6/79 (8%) cases post-intervention ($p=0.35$). Where there was not a final diagnosis of CAP ($n=28$), 12 patients (3/8 pre-intervention, 9/20 post-intervention) received initial treatment with a ceftriaxone-based regimen.

Documentation of severity scores and compliance of initial antibiotic choice with the guidelines (according to severity score) increased post-intervention, compared with the pre-intervention levels, but those differences did not reach statistical significance (Table 3.2). Where antibiotic therapy did not match guidelines, 7/9 (78%) patients received ceftriaxone plus azithromycin in non-severe pneumonia pre-intervention, compared with 11/17 (65%) post-intervention. Benzylpenicillin was administered for severe CAP once in each cohort, where the guidelines recommended ceftriaxone. There were no significant differences in LOS, 30-day readmission rate or in-hospital mortality between the two groups (Table 3.2). One included patient was treated by a study investigator (WY).

Table 3.2: Outcomes in patients with a final diagnosis of community-acquired pneumonia

Variable	Pre-intervention (2013) (n=34)	Post- intervention (2014) (n=79)	p value
Total duration of antibiotic therapy, median (IQR), days	11 (9-13)	9 (7-10)	0.04
Duration of intravenous antibiotic therapy, median (IQR), days†	3 (2-5)	3 (2-5)	0.74
Severity score documented, n (%) ‡	11 (32)	35 (44)	0.22
Mild-mod receiving initial ceftriaxone, n (%) –excluding penicillin allergy§	14 (74)	18 (45)	0.04
Initial antibiotics guideline compliant (“completely”), n (%)	11 (30)	32 (41)	0.41
Therapy escalated by admitting team, n (%) ¶	2 (6)	12 (15)	0.22
Length of stay, median (IQR) days	6 (3-10)	6 (3-12)	0.74
30 day readmissions, n (%)	4 (12)	13 (16)	0.77
In-hospital mortality	2 (6)	4 (5)	1

†31 known pre-intervention, 79 post-intervention; ‡34 known pre-intervention, 78 known post-intervention; §19 known pre-intervention, 40 known post-intervention; ¶pre-intervention, benzylpenicillin to ceftriaxone (n=1), ceftriaxone to meropenem (n=1); post-intervention, benzylpenicillin to ceftriaxone (n=6), ceftriaxone to piperacillin/tazobactam (n=4), ceftriaxone to ciprofloxacin (n=2); 30 day readmissions, 1 for pneumonia pre-intervention, 2 for pneumonia post-intervention.

Email responses were received for 20 of 99 sent emails; 6 from AMOs and 14 from junior medical staff. The responses either contained clinical feedback (17/20) or acknowledged the email (3/20); there were no defensive responses.

3.6 Discussion

Our study demonstrated that an intervention combining education with audit and email feedback was associated with a significant reduction in the median duration of total antibiotic therapy from 11 to 9 days that was driven by shorter courses of oral therapy. The number of patients with non-severe CAP receiving a ceftriaxone-based regimen also decreased significantly (74% to 45%). Increases of almost 30% in documentation of severity score and compliance with guidelines were observed, although these did not reach statistical significance.

Previous AMS studies have reported similar reductions in duration of IV (Fine et al., 2003; Carratala et al., 2012) and total antibiotic therapy (Avdic et al., 2012). Our study differed in that we targeted emergency medicine to address initial treatment, and admitting teams for ongoing therapy. We also demonstrated an approach applicable to rural and regional hospitals, through use of a CDSS-supported ASP, the eMR and email feedback. Feedback of results was provided on an individual case basis, which may be more effective if clinicians have previously agreed to review practice (Ivers et al., 2012). Emails to doctors were broadly well received.

Our study had several limitations, including its single-centre design and small number of patients. The change to data collection methodology post-intervention may have resulted in a change to patient demographics, even though the same screening criteria were used. Discharge dispensing data were obtained from pharmacy and outpatient compliance was not evaluated. Parameters for calculation of SMART-COP scores were not available in 14% of cases, thus disease severity may have been underestimated in those patients. Patients with treatment limitations were not excluded, which may have resulted in worse patient outcomes; however, antibiotics are typically not withheld in those patients, and inclusion criteria did not change between study periods. The response rate to emails was low; however, email was not used as the only feedback method, with departmental meetings and daily AMS rounds forming part of the education strategy.

The intervention demonstrated a reduction in duration of therapy that was driven by shorter courses of oral antibiotics. Median duration of total therapy remained long at 9 days, indicating that further interventions are required to address both duration of therapy and LOS. Post-intervention, some patients still received ceftriaxone for non-severe CAP but the frequency was significantly reduced. Although the exact reasoning behind ceftriaxone overuse cannot be inferred from our data, possible reasons include its once daily administration, broad spectrum, lack of requirement for dose adjustment and existence of sepsis guidelines. Although it was recognised that therapy should be reviewed following discharge from ED, there may still have been some prescribing etiquette shown by admitting medical teams, with an unwillingness to change a therapy in an improving patient (Charani et al., 2013).

3.6.1 Conclusions

We have demonstrated significant reductions in total duration of CAP therapy and of inappropriate ceftriaxone-based therapy for non-severe CAP following a targeted intervention that combined education with audit and feedback. This approach addressed initial and ongoing prescribing, and may be readily transferred to other settings. Ongoing education with timely feedback of audit results is recommended to foster sustainability.

3.6.2 Acknowledgements

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4 The burden of healthcare associated *Clostridium difficile* infection in a non-metropolitan setting

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4.1 Summary statement

The themes of multisite and rural/regional applicability of AMS initiatives are explored in this chapter, which relates to CDI, a serious adverse effect of antimicrobial use. Using a multisite approach, the outcomes of patients complicated by healthcare-associated CDI are investigated. The widespread use of antimicrobials across the health district, and geographic disparity of the hospitals, necessitated the use of email feedback and education, which builds on those themes described in Chapters 2 and 3. The use of technology (CDSS and e-learning tool) to provide pragmatic AMS education is further explored in Chapters 5, 6 and 7.

4.2 Abstract

4.2.1 Objective

CDI is a major cause of healthcare associated (HCA) diarrhoea in industrialised countries and is associated with considerable morbidity and mortality. No data exist on the burden of HCA-CDI in multisite non-metropolitan settings. This study examined the introduction of an ASP in relation to HCA-CDI rates and the effect of HCA-CDI on LOS and hospital costs.

4.2.2 Methods

A before-and-after intervention comparative study of patients aged 16 years and over with HCA-CDI from December 2010 to April 2016 across the nine hospitals of a non-metropolitan health district in NSW, Australia. The intervention comprised a multisite ASP supported by a CDSS, with subsequent introduction of email feedback of HCA-CDI cases to AMOs. Main outcome measures: HCA-CDI rates; comparative LOS and hospital costs; prior antimicrobial and proton-pump inhibitor (PPI) use; appropriateness of CDI treatment.

4.2.3 Results

HCA-CDI rates rose from 3.07 to 4.60 cases per 10,000 occupied bed days (OBDs) pre-intervention, and remained stable at four cases per 10,000 OBDs post-intervention ($p=0.24$). Median LOS (17 vs. 6 days, $p<0.01$) and hospital costs (AU\$19,222 vs. \$7,861, $p<0.01$) were significantly greater for HCA-CDI cases ($n=91$) than for matched controls

(n=172). Half of the patients with severe HCA-CDI (4/8) did not receive initial appropriate treatment (oral vancomycin).

4.2.4 Conclusions

HCA-CDI placed a significant burden on our regional and rural health service through increased LOS and hospital costs. Interventions targeting HCA-CDI could be employed to consolidate the effects of ASPs.

4.2.5 Keywords

Clostridium difficile infection, antimicrobial stewardship, antibiotics, length of stay, hospital costs

4.3 Introduction

CDI is a major cause of HCA diarrhoea in industrialised countries and is associated with considerable morbidity and mortality (Valiquette et al., 2007). In Australia, the annual incidence of hospital-identified CDI was 4.03 cases/10,000 patient days in 2012 (Slimings et al., 2014). Risk is increased by antimicrobial use and/or immunosuppression (Cheng et al., 2011). Other putative risk factors include gastrointestinal surgery, gastric acid-suppressive therapy and prolonged hospital stay (Cheng et al., 2011).

HCA-CDI has been associated with increased LOS, additional costs from hospitalisation (Gabriel and Beriot-Mathiot, 2014) and antimicrobial treatment (Cheng et al., 2011), and indirect costs such as productivity losses (McGlone et al., 2012).

Most antimicrobials have been related to occurrence of CDI, with lincosamides (e.g. clindamycin), third generation cephalosporins (e.g. ceftriaxone), and broad-spectrum penicillins (e.g. amoxycillin/clavulanic acid) showing strong associations (Slimings and Riley, 2014). Fluoroquinolones have been particularly associated with the hypervirulent NAP1/027 strain (Vardakas et al., 2012). There is probable association between PPI use and CDI, with the combination of PPIs and antimicrobials carrying a greater risk than either alone (Kwok et al., 2012).

ASPs should be employed to reduce the incidence of HCA-CDI (Valiquette et al., 2007). Despite HCA-CDI being an outcome measure for ASPs, increasing community acquisition of CDI may cloud interpretation of HCA-CDI rates (Slimings et al., 2014).

AMS interventions targeting HCA-CDI have predominantly been conducted in metropolitan teaching hospitals, at single sites or within a defined clinical area (Talpaert et al., 2011; Feazel et al., 2014; Vonberg et al., 2008; Thomas and Riley, 2003; Brumley et al., 2016). Very limited data exist on the burden of HCA-CDI in Australia, particularly in regional and rural settings (Riley et al., 1995). To our knowledge this is the first study to examine a multisite ASP in relation to HCA-CDI rates in the non-metropolitan setting.

The aims of our study were: to describe HCA-CDI rates before and after an ASP; to measure LOS and hospital costs in HCA-CDI patients across multiple hospital sites; to compare prior antimicrobial and PPI use in HCA-CDI patients with the background use; and to assess appropriateness of HCA-CDI antimicrobial treatment according to guidelines.

4.4 Methods

4.4.1 Setting

From December 2010 to April 2016, a study on the burden of HCA-CDI was performed across the nine public hospitals (1000 total beds) of ISLHD in south eastern NSW, Australia. The district services 390,000 residents across a catchment that begins one hour south of Sydney, and extends 250km along a coastal strip. The three largest hospitals comprise one principal referral hospital (550 beds), a large acute hospital (150 beds) and a medium acute hospital (100 beds). The remaining six hospitals are either small acute or mixed sub- and non-acute (Australian Institute of Health and Welfare, 2015). This study

employed PDSA quality improvement methodology (National Health Service Institute for Innovation and Improvement, 2008).

4.4.2 Antimicrobial stewardship

In May and June 2012, an ASP supported by a CDSS (GuidanceMS[®]) (Guidance Group, 2013) was uniformly implemented across the district's nine hospitals. The CDSS enabled monitoring of antimicrobial use and facilitated regular AMS rounds where advice on appropriate antimicrobial use could be offered by an ID physician and pharmacist (post-prescription review). In addition to the CDSS, the ASP involved a restriction policy, whereby broad spectrum antimicrobials were only stocked in pharmacy (with supply contingent on CDSS approval) or specialist areas (i.e. intensive care unit [ICU], ED, haematology/oncology ward). Those antimicrobials included third generation cephalosporins, intravenous beta/lactamase inhibitor combinations and fluoroquinolones. Additional restriction (prior ID/microbiology approval required) was placed on reserve antimicrobials such as linezolid, daptomycin, tigecycline and colistimethate sodium. An education campaign involved regular departmental presentations, and an intranet webpage was established to improve access to guidelines. In addition to regular AMS rounds at the three largest hospitals, and an antimicrobial advice telephone hotline was established across the district to support the smaller hospitals without onsite AMS clinicians. See Figure 4.1 for the study flowchart. There were no major changes to infection control policies related to either *Clostridium difficile* or hand hygiene during the study period. Patients in whom *Clostridium difficile* was detected were routinely isolated in single rooms, and personal protective equipment (disposable gown and gloves) was mandated by infection control policy.

Following a review of HCA-CDI rates, in April 2013 the AMS team (infectious diseases doctors and pharmacists) introduced a targeted CDI intervention. The AMS pharmacist audited all CDI cases for the following: patient demographics, risk factors, antimicrobial treatment, features indicating severe disease (Cheng et al., 2011), ICU admission, surgical intervention, and NAP1/027 strain. A feedback email was then sent to the attending medical officer (AMO) within two weeks (Figure 4.2). Qualitative analysis of email responses determined the level of acceptance by AMOs. Responses were categorised as clinical feedback, basic acknowledgement or defensive. The appropriateness of HCA-CDI treatment (Cheng et al., 2011) was assessed during AMS rounds or retrospectively from medical notes. Results were presented to the AMS, drug and therapeutics, and infection control committees.

4.4.3 *Clostridium difficile* laboratory testing

From December 2010, our laboratory protocol subjected all diarrhoeal stools to *Clostridium difficile* testing. First line testing targeted glutamate dehydrogenase (GDH) antigen and toxins A and B (C. Diff Quik Chek Complete®, Techlab, Blacksburg, VA, USA). If those tests were discordant, then a polymerase chain reaction (PCR; GeneXpert®, Cepheid, Sunnyvale, CA, USA) test was employed, which could also detect the NAP1/027 strain. During the period June to November 2015, HCA *Clostridium difficile* stool samples were sent to a reference laboratory for molecular typing as part of a larger project examining HCA-CDI rates. No clonal similarities were identified, and molecular epidemiology was similar to other parts of NSW (data not shown).

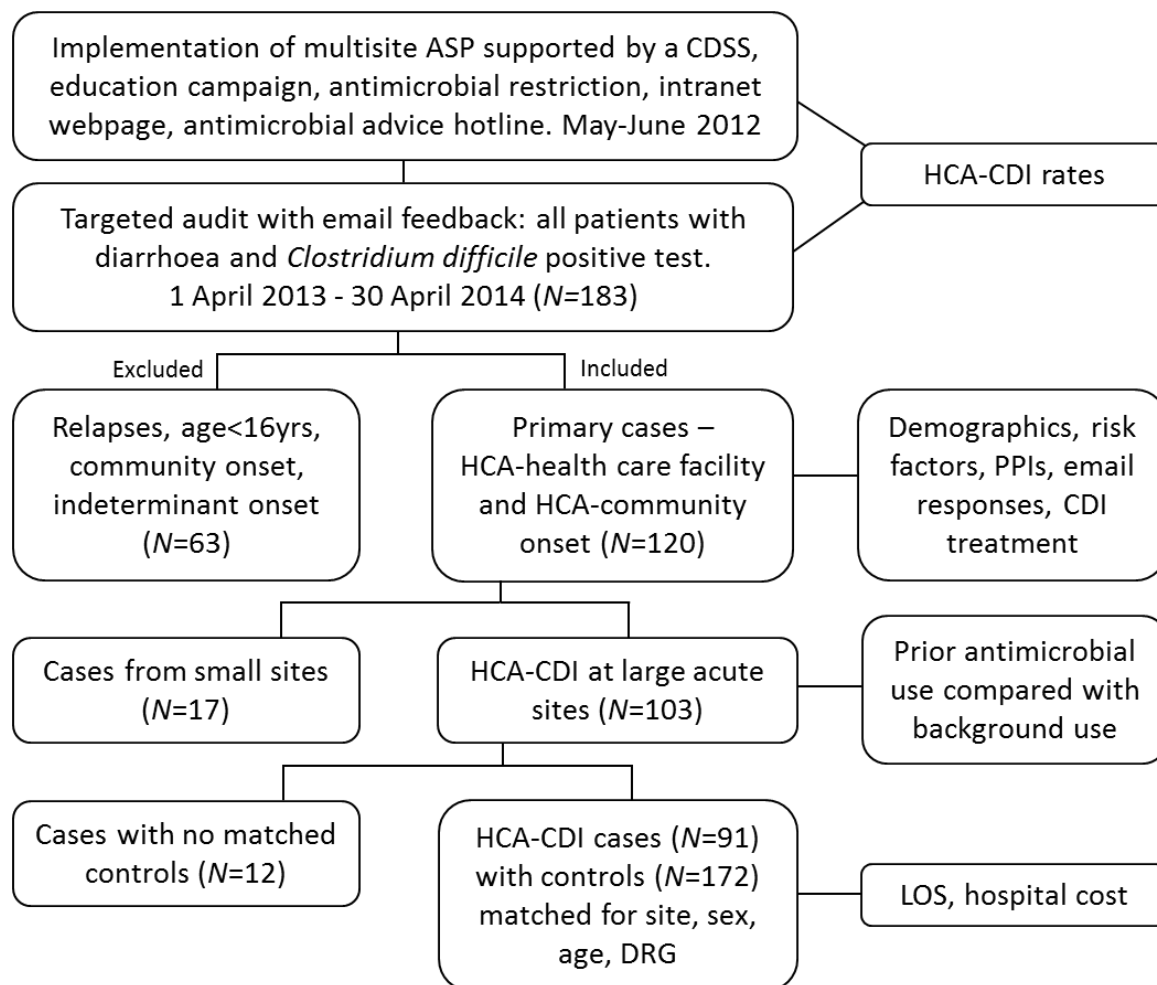


Figure 4.1: Study flowchart

Abbreviations: ASP, antimicrobial stewardship program; CDSS, clinical decision support system; HCA, healthcare associated; LOS, length of stay; risk factors, anti-peristaltic use, gastrointestinal surgery, immunosuppression; PPIs, proton pump inhibitors; HCA-CDI, healthcare associated *Clostridium difficile* infection; DRG, diagnosis-related group; background use, whole hospital prevalence data on antimicrobial use

Dear Doctor,

As part of routine antimicrobial stewardship activities we are conducting a prospective audit into all episodes of C. diff diarrhoea across the district.

Your patient X (MRN: 111111) was diagnosed with C. diff diarrhoea on dd/mm/yyyy.

Potential risk factors for your patient included:

(As appropriate)

- Proton pump inhibitor use –
- Anti-peristaltic use –
- Prior GI surgery –
- Immunosuppression –
- Antimicrobial use within one month prior to diagnosis –

Details of antimicrobial treatment of CDI.

I've attached a copy of the audit form for your information. Please don't hesitate to contact me if you have any questions.

Regards,

AMS pharmacist

Figure 4.2: CDI exemplar feedback email to admitting medical officer

4.4.4 Effect of HCA-CDI on LOS and hospital costs

LOS and hospital cost analysis was performed only for the three acute hospitals due to a shortage of matched controls and other confounders for LOS at smaller hospitals (e.g. nursing home availability, social factors). The two definitions for HCA-CDI were: HCA-healthcare facility onset, diarrhoea onset >48 hours after admission; HCA-community onset, diarrhoea onset in the community or <48 hours after admission, but within four weeks of last discharge (Healthcare Associated Infection Technical Working Group, 2013). Demographic data for HCA-CDI cases did not differ significantly between hospitals, or between the two types of HCA-CDI (data not shown), so all HCA-CDI cases were included for further analysis, including healthcare facility (n=103) and community onset (n=17; Figure 4.1).

A post hoc analysis of LOS and hospital costs was conducted for those HCA-CDI cases identified from 1 April 2013 to 30 April 2014. Matched controls were identified from diagnosis-related group (DRG) data (Australian Institute of Health and Welfare, 2016) for HCA-CDI cases (n=103). Controls were identified from 1 January 2013 to 30 June 2014. Two controls were matched to each case by site, sex, age (+/- 5 years), and DRG (81 cases). Where two matched controls were not available, one control was identified (10 cases), resulting in 91 cases and 172 controls (Figure 4.1). DRGs were grouped and the most common DRGs were reported. Additional analysis was performed on those HCA-CDI cases and controls with LOS of ≥ 8 days to address time-dependent biases (8 days equalled the median time to HCA-CDI onset).

4.4.5 Antimicrobial and PPI use

Antimicrobial use within one month prior to diagnosis among HCA-CDI patients was compared with background antimicrobial use data, regularly collected in Australia as part of standard surveillance reports. Those data (defined daily doses [DDD] per 1000 OBDs) from the three acute hospitals were derived from the Australian National Antimicrobial Utilisation Surveillance Program (NAUSP; from pharmacy software) and the Australian National Antimicrobial Prescribing Survey (NAPS; point prevalence survey in November 2013, seasonally corrected, antimicrobial class use as a percentage of total use). PPI use was also compared with background use (point prevalence survey 2013).

4.4.6 Statistical analyses

ITS analysis (Linden, 2015) was used to assess HCA-CDI rates at the three large hospitals (due to comparability of acute OBD data). Data were included from December 2010 (earliest time point with current CDI testing methods) to April 2016, with the intervention point defined as May 2012 (introduction of multisite ASP). Separate analyses were performed for May 2012- Mar 2013 and April 2013 onwards (targeted CDI intervention). Since those periods did not reveal any significant differences (data not shown) the post-intervention period was reported as one interval. A chi-square test was used for proportions or Fisher's exact test where appropriate. A Mann-Whitney U-test was used to compare continuous variables such as LOS and hospital costs. Stata[®] Statistical Software Version 14 was used (Statacorp, College Station, Texas, USA). Significance was accepted as $p < 0.05$.

4.4.7 Ethics

Ethics approval was received from the joint UOW and ISLHD Human Research Ethics Committee, approval number HE13/137 (Appendix D).

4.5 Results

Figure 4.3 shows ITS analysis of monthly HCA-CDI rates. The model-predicted HCA-CDI rate in December 2010 was 3.07 cases/10,000 OBDs. Prior to introduction of the ASP, the model-predicted rate was 4.6 cases/10,000 OBDs. Following the ASP's introduction, and including the targeted email intervention, HCA-CDI rates remained stable at 4 cases/10,000 OBDs. None of those differences reached statistical significance, demonstrating an overall stable rate of HCA-CDI during the study period. The principal referral hospital accounted for two thirds of the health district's inpatient activity, and so largely drove the overall HCA-CDI rate. There was larger monthly variability in HCA-CDI rates at the smaller sites, but no significant differences in overall rates between sites. Detailed ITS data are provided in Table 4.1.

During the targeted intervention phase from April 2013 to April 2014, 120 primary HCA-CDI cases were identified. The median age was 73 years (IQR 63-81yrs) and 51/120 (43%) of patients were male. Antimicrobials one month prior to HCA-CDI diagnosis were received by 107/120 (89%) patients. Severe disease was identified in 8/120 (7%) cases; there were 8/120 (7%) ICU admissions, no surgical interventions, and no

NAP1/027 strains. Following a positive test for *Clostridium difficile*, all patients were isolated in single rooms according to policy.

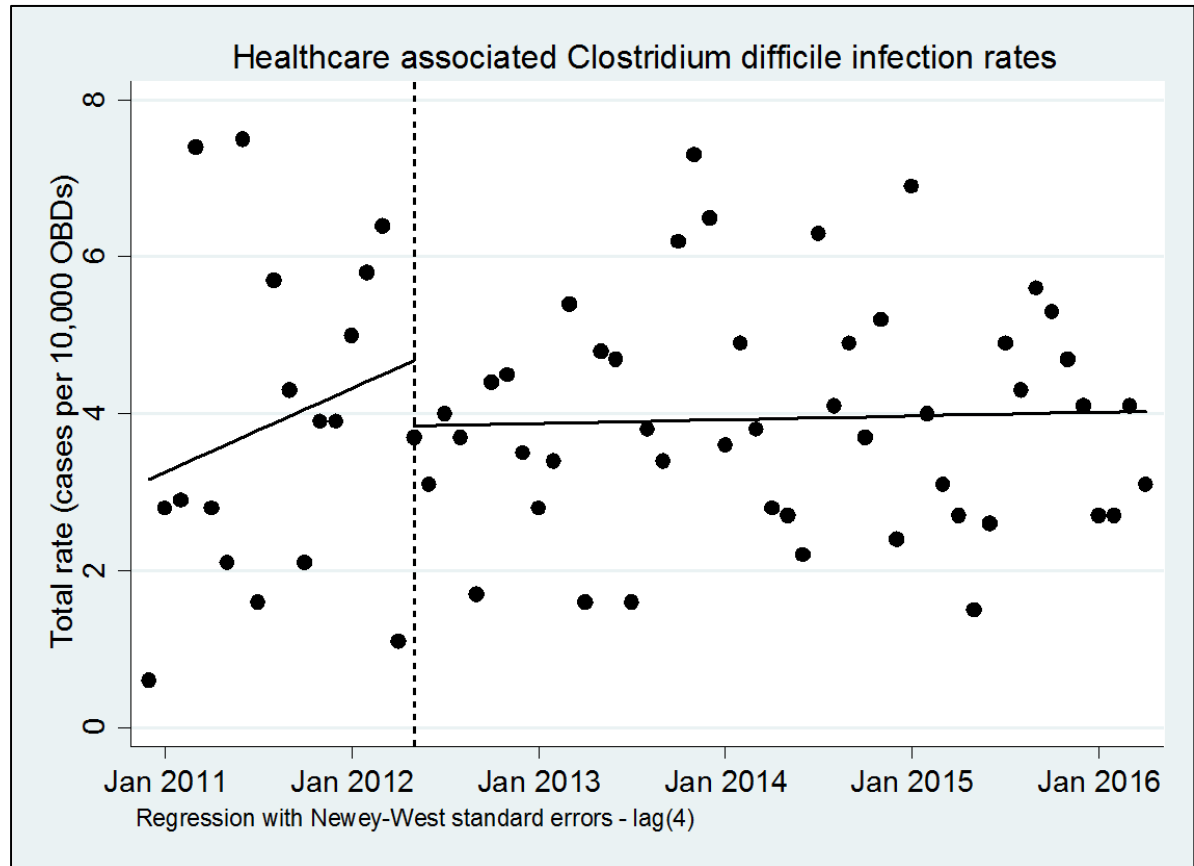


Figure 4.3: HCA-CDI rates for the three acute hospitals in Illawarra Shoalhaven Local Health District, Australia from December 2010 to April 2016

Vertical line, implementation of antimicrobial stewardship program; HCA-CDI, healthcare associated *Clostridium difficile* infection; OBD, occupied bed day.

Table 4.1: HCA-CDI rates before and after implementation of an ASP

	Pre-ASP			Post-ASP			
	(Dec 2010 to April 2012)			(May 2012 to April 2016)			
	Initial level	Initial trend	p value	Change in level	p value	Change in trend	p value
HCA CDI per	3.07 ^a	0.09 ^a	0.23	-0.83 ^a	0.24	-0.08 ^a	0.26
10,000 OBDs, n	(1.51-	(-0.06-		(-2.25-		(-0.24-	
(LCI, UCI)	4.65)	0.24)		0.58)		0.07)	

Initial level, number of cases of HCA-CDI per 10,000 occupied bed days per month; initial trend, rate of increase per month; change in level, immediate difference between pre-intervention and post-intervention cases; change in trend, difference between pre-intervention and post-intervention trend by month; ASP, antimicrobial stewardship program, detail described in Methods; HCA-CDI, healthcare associated *Clostridium difficile* infection, data included for the three large acute hospitals of the health district; OBDs, occupied bed days; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval; ^aadjusted for first order autocorrelation;

Of the emails sent to AMOs for 120 HCA-CDI cases from April 2013-14, 23 responses were received (19% response rate). Of those responses, 10 contained clinical feedback, 13 contained basic acknowledgement, and there were no defensive responses. Examples of clinical feedback responses were: “...in the setting of immune suppression and...other complications with chemo I am treating C diff...”; and, “the (antibiotic) was for aspiration... the PPI (was) longstanding...”.

Median LOS was 11 days greater for HCA-CDI patients (n=91; 17 days [IQR 8-27]) than their matched controls (n=172; 6 days [IQR 3-12]; p<0.01). Also, median hospital cost was estimated at AU\$11,361 higher for the HCA-CDI group (\$19,222 [IQR \$7,817 - \$41,337]) compared to controls (\$7,861 [IQR \$3,477 - \$14,553]; p<0.01). The median time to onset of HCA-CDI was 8 days (IQR 4-14).

The median hospital cost for 48 HCA-CDI patients with LOS \geq 8 days was AU\$17,832 (IQR 9,472-28,840) vs. AU\$12,563 (9,072-20,086) for 70 controls with LOS \geq 8 days (p=0.17). For patients with LOS \geq 8 days, the median LOS was 16 days (IQR 10-26) for HCA-CDI cases vs. 15 days (IQR 12-26) for controls. After excluding non-treated patients (n=6) with available controls (n=11), the difference between HCA-CDI patients and controls persisted for median LOS (18 vs. 7 days; p<0.01) and cost (AU\$20,245 vs. \$8,924; p<0.01). The five most common primary DRGs among 263 HCA-CDI cases and controls were: gastrointestinal (n=18 for cases, n=36 for controls), haematological malignancy (n=9, n=17), orthopaedic surgery (n=8, n=15), abdominal surgery (n=6, n=10), and cardiac (n=5, n=9).

Antimicrobial use among the HCA-CDI group at the three acute hospitals was compared with background antimicrobial use (Figure 4.4). Over-represented in HCA-CDI patients were third generation cephalosporins (e.g. ceftriaxone; 34% of total use in HCA-CDI patients vs. 11% of background use; p<0.01), beta-lactamase inhibitor combinations (e.g. piperacillin/tazobactam; 58% vs. 36%; p=0.01), nitroimidazoles (e.g. metronidazole; 28% vs. 11%; p<0.01), and glycopeptides (e.g. vancomycin; 23% vs. 6%; p<0.01). Under-represented in HCA-CDI patients were beta lactamase resistant penicillins (e.g.

flucloxacillin; 7% vs. 18%; $p=0.02$), beta lactamase sensitive penicillins (e.g. benzylpenicillin; 2% vs. 9%; $p=0.03$), extended spectrum penicillins (e.g. ampicillin; 14% vs. 33%; $p=0.03$), macrolides (e.g. azithromycin; 4% vs. 19%; $p<0.01$), and tetracyclines (e.g. doxycycline; 4% vs. 38%; $p<0.01$). Implementation of the multisite ASP was associated with an overall decrease in use of broad spectrum antimicrobials (e.g. third generation cephalosporins, fluoroquinolones and intravenous beta/lactamase inhibitor combinations; data not shown). Reporting on temporal changes to antimicrobial use patterns was beyond the scope of this study.

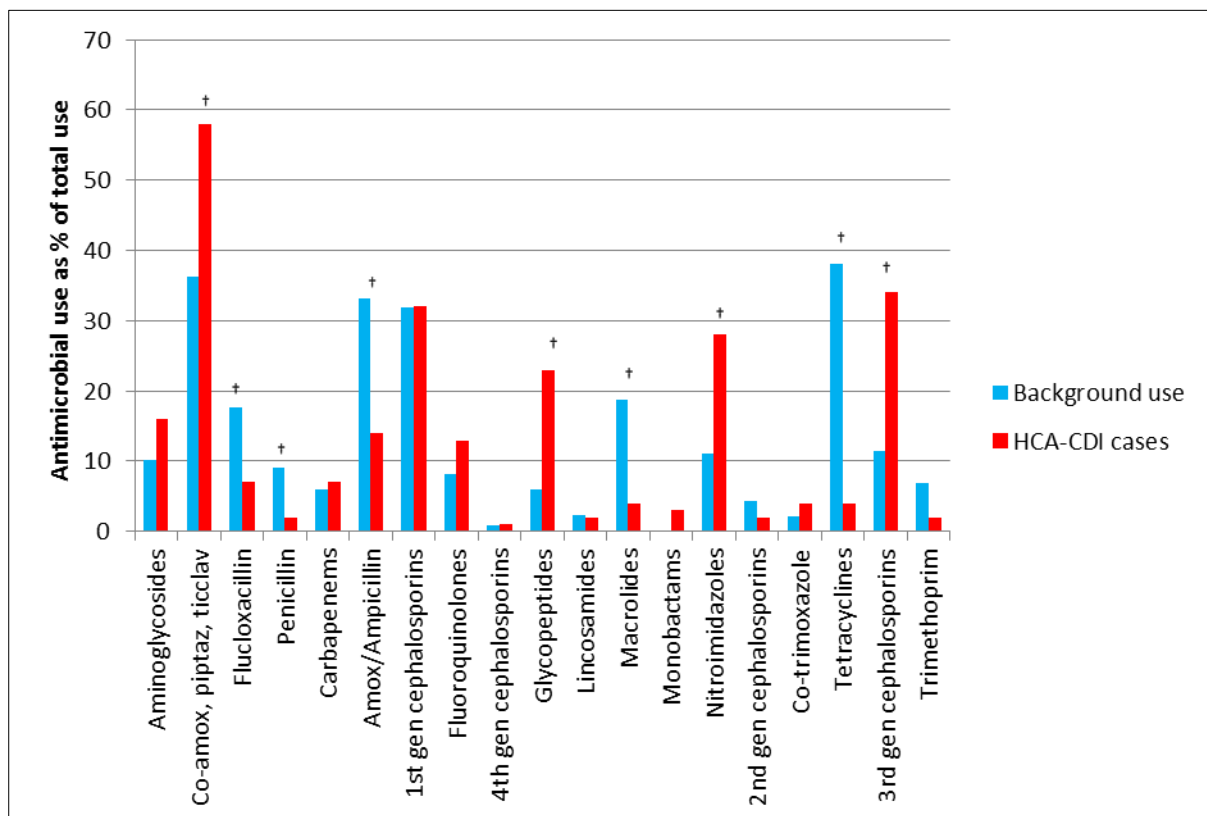


Figure 4.4: Antimicrobial use for HCA-CDI cases compared with background

antimicrobial use

†Denotes statistical significance

Vancomycin and metronidazole were over-represented in HCA-CDI patients, but are also recommended for CDI treatment. Those two classes were further analysed. For vancomycin, the most commonly co-prescribed antimicrobial was piperacillin/tazobactam (11/25) with febrile neutropenia the commonest known indication (9/11). Vancomycin use was intravenous in all of those cases. For metronidazole, the most commonly co-prescribed antimicrobial was ceftriaxone (13/35), predominantly for abdominal infections (10/13). There was an overall decrease in use of broad spectrum antimicrobials following implementation of the multisite ASP (data not shown). PPI use was documented in 83/120 (69%) HCA-CDI patients compared with 343/730 (47%) patients audited as part of a local 2013 point prevalence survey ($p < 0.01$).

In non-severe HCA-CDI treated at the acute hospitals ($n=95$), oral metronidazole was initiated in 78 (82%) cases. Oral vancomycin plus oral metronidazole was used in eight (8%) cases, where metronidazole alone would have sufficed (Cheng et al., 2011). No therapy was given in nine non-severe cases, due to cessation of diarrhoea with or without identification of an alternative correctable cause. In the severe HCA-CDI group ($n=8$), oral metronidazole was initiated in 4 (50%) cases, where oral vancomycin, intravenous metronidazole or a combination was indicated. In those cases a relevant AMS intervention was made.

4.6 Discussion

Our study describes the relationship between HCA-CDI rates and a multisite ASP supported by a CDSS, education and antimicrobial restriction combined with targeted

audit and feedback. The effect of the ASP on HCA-CDI rates did not reach statistical significance, demonstrating that HCA-CDI rates remained stable during the study period. Targeted interventions may help to combat the waning of the initial impact of a program over time. We found that in an Australian non-metropolitan setting, LOS and hospital costs were significantly increased in HCA-CDI patients when compared with matched controls. Increased antimicrobial and PPI use in patients with HCA-CDI were consistent with previous reports (Slimings and Riley, 2014; Kwok et al., 2012). Although the initial treatment of non-severe HCA-CDI cases predominantly matched guidelines, there was concerning use of oral metronidazole in half of the severe cases (albeit with small numbers). This was similar to previous findings elsewhere (Jury et al., 2013), likely resulting from under-recognition of severity criteria (Cheng et al., 2011; Trubiano et al., 2016).

HCA-CDI has been associated with increased LOS and hospital costs (Gabriel and Beriot-Mathiot, 2014). Most studies evaluating these effects were either epidemiological studies (Pakyz et al., 2011; Campbell et al., 2013) or performed in the metropolitan setting (Feazel et al., 2014). To our knowledge this is the first study to combine evaluation of the burden of HCA-CDI with multisite ASP implementation in a regional and rural setting. Comparison with matched controls allowed for a pragmatic approach to identifying additional LOS and hospital costs associated with HCA-CDI (Kyne et al., 2002; Vonberg et al., 2008). For those patients with $\text{LOS} \geq 8$ days, there was a 42% increase in hospital costs in HCA-CDI patients compared with controls, despite similar LOS in those groups. This highlighted the increased cost of caring for HCA-CDI patients additional to greater LOS, and alleviated the potential for time-dependent biases.

There were several limitations to this study. We included all positive *Clostridium difficile* tests during the targeted intervention phase, as the frequency of daily diarrhoeal episodes was unreliably documented. Alternative causes of diarrhoea may have been present in some patients carrying *Clostridium difficile*. We could not attribute the increase in LOS and hospital costs to HCA-CDI alone. Alternative statistical methods such as multi-state modelling (van Kleef et al., 2014) to account for time-dependent biases, and propensity matching (Gabriel and Beriot-Mathiot, 2014) to accurately estimate the impacts of CDI have been proposed. To account for those limitations, we applied the case-control methodology in two additional subsets: the “long-stay” patients (≥ 8 days, the median time-to-onset of HCA-CDI) and only those treated for HCA-CDI. Those results were in line with our primary evaluation, emphasising the high LOS and cost burden of HCA-CDI. As expected, gastrointestinal DRGs were overrepresented. In some cases the primary DRG may have been allocated to gastrointestinal due to CDI severity or duration.

Community cases could not be accurately assessed with the current study resources. Of 120 HCA-CDI cases, only 91 were eventually analysed for LOS and cost. Assessing the impact on HCA-CDI rates might have been confounded for antimicrobials (e.g. metronidazole, vancomycin) often given to treat CDI or co-administered with antimicrobials associated with HCA-CDI. Intravenous vancomycin has been associated with CDI (Hecht and Olinger, 1989); however, vancomycin was associated with CDI in this study only when combined with other antimicrobials. We did not evaluate appropriateness of prior antimicrobial use, in order to define avoidable HCA-CDI cases. Detailed demographic data and prior antimicrobial use were not collected for controls, as

this dataset was collected to allow for a post hoc analysis. Using background antimicrobial and PPI data allowed for larger numbers and accounted for the potential of bias due to under-reporting of those agents in control patients in whom CDI was not considered. However, detailed characteristics of patients from whom the background use data were derived were not available. The largest hospital accounted for two thirds of the total OBDs; hence its infection rate largely determined the overall rate. The response rate to emails was only 19%, limiting conclusions about their impact; however, responses were not requested in the initial email, and still some useful clinical feedback was received. Due to the hospitals' geographic disparity, email remained the most pragmatic feedback method.

Patient complexity in our hospitals may be lower compared with larger metropolitan hospitals, limiting generalisability to those settings. Further studies combining evaluation of ASPs with targeted CDI interventions would be useful, particularly in multisite and non-metropolitan settings. In this study we identified high risk antimicrobial classes that have formed targets for ongoing AMS activities.

4.6.1 Conclusions

Our study demonstrates the high burden of HCA-CDI in a non-metropolitan setting. While it confirms the association between high-risk antimicrobial use and HCA-CDI, it also identifies the possibility of under-recognition of CDI severity criteria during treatment initiation. Targeted audit and feedback interventions may be a useful way of consolidating the effects of a multisite ASP, contributing to sustainability, which remains one of the major challenges of contemporary AMS.

4.6.2 Acknowledgements

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Conflicts of interest

None declared.

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5 Outcomes of multisite antimicrobial stewardship program implementation with a shared clinical decision support system

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5.1 Summary statement

This chapter provides an insight into the challenges associated with evaluating ASP implementation (involving an education campaign) across multiple hospital sites and health districts. The theme of multisite AMS education supported by technology is further explored in Chapters 6 and 7. Varying resources between hospitals necessitated a combined approach, whereby implementation was based around a CDSS and allowed for AMS support to be provided to the smaller and more remote sites with less on-site expertise. An evidence gap was identified around centrally-deployed decision support

technology to facilitate improved antimicrobial use. At a multi-health district level, CDI, infection-related LOS and mortality were examined as outcome measures for the ASP. Measurement of outcomes related to antimicrobial use was also explored in Chapter 2 (renal toxicity and SSIs), Chapter 3 (30 day readmission rate and in-hospital mortality), and Chapter 4 (CDI).

All results tables are provided at the end of the chapter (pages 148-161).

5.2 Abstract

5.2.1 Objective

Studies evaluating ASPs supported by CDSSs have predominantly been conducted in single site metropolitan hospitals. This study aimed to examine outcomes of multisite ASP implementation supported by a centrally deployed CDSS.

5.2.2 Methods

An ITS study of a CDSS-supported multisite ASP was conducted across five hospitals in NSW, Australia from 2010 to 2014. Outcomes analysed were: effect of the intervention on targeted antimicrobial use, antimicrobial costs, HCA-CDI rates, infection-related LOS, and standardised mortality ratios (SMRs).

5.2.3 Results

Post-intervention, antimicrobials targeted for increased use rose from 223 to 293 DDDs/1000 OBDs/month (+32%, $p < 0.01$). Conversely, antimicrobials targeted for

decreased use fell from 254 to 196 DDDs/1000 OBDs/month (-23%; $p<0.01$). These effects diminished over time. Antimicrobial costs decreased initially (-AU\$64,551/month; $p<0.01$), then increased (+AU\$7,273/month; $p<0.01$). HCA-CDI rates decreased post-intervention (-0.2 cases/10,000 OBDs/month; $p<0.01$). Proportional LOS reductions for key infections (respiratory 4.8 to 4.3 days, $p<0.01$; septicaemia 6.8 to 6.1 days, $p<0.01$) were similar to background LOS reductions (2.1 to 1.9 days). Similarly, infection-related SMRs (observed/expected deaths) decreased in line with background rates (respiratory 1.1 to 0.75; septicaemia 1.25 to 0.8; background rate 1.19 to 0.90).

5.2.4 Conclusions

Implementation of collaborative multisite ASP supported by a centrally deployed CDSS was associated with changes in targeted antimicrobial use, decreased antimicrobial costs, decreased HCA-CDI rates, and no observable increase in LOS or mortality. Ongoing targeted interventions are suggested to promote sustainability.

5.2.5 Keywords

Antimicrobial stewardship, computerised clinical decision support system, health costs, *Clostridium difficile*, length of stay, mortality rate

5.3 Introduction

ASPs aim to improve appropriateness of antimicrobial prescribing with the goals of more effectively treating and preventing infections, while curbing AMR and reducing adverse effects (Duguid and Cruickshank, 2010; Barlam et al., 2016). Studies examining the impact of ASPs have primarily been conducted in tertiary metropolitan hospitals (Cairns et al., 2013; Sick et al., 2013; Standiford et al., 2012; Nowak et al., 2012; Baysari et al., 2016; Schuts et al., 2016). There is limited literature describing clinical outcomes from collaboratively implemented ASPs across multiple hospital sites (Ostrowsky et al., 2014; Lai et al., 2016; Cosgrove et al., 2012; Schuts et al., 2016). Previous single site ASP studies have demonstrated benefits using a CDSS, antimicrobial restriction, and prospective audit and feedback (Cairns et al., 2013; Sick et al., 2013; Nowak et al., 2012; Standiford et al., 2012; Davey et al., 2013). These benefits include a reduction in targeted antimicrobial use (Davey et al., 2013; Carling et al., 2003; Sick et al., 2013), antimicrobial drug acquisition costs (Ansari et al., 2003; Carling et al., 2003; Sick et al., 2013), and HCA-CDI rates (Aldeyab et al., 2012; Carling et al., 2003). An evidence gap exists for implementation of ASPs across multiple sites using a centrally deployed CDSS (Barlam et al., 2016).

Metrics for evaluating ASPs include antimicrobial use, drug costs, adverse effects such as HCA-CDI and AMR, LOS, and mortality (Morris et al., 2012; Khadem et al., 2012).

Infection-related outcomes related to CAP, skin and soft tissue infections and septicemia have been also been recommended (Morris et al., 2012). Although there are confounders

associated with their use as ASP metrics, LOS and mortality are useful balancing measures to address potential unintended consequences (Davey et al., 2013).

To our knowledge, no studies of multisite ASPs using a centrally deployed CDSS have included non-metropolitan hospitals. The aims of this study were to evaluate the impact of a CDSS-supported, multisite ASP on antimicrobial use, antimicrobial costs, HCA-CDI rates, infection-related LOS, and SMRs.

5.4 Methods

5.4.1 Setting

In 2012 a multisite ASP supported by a centrally deployed CDSS was implemented in 12 hospital sites (Figure 5.1) across the South Eastern Sydney and Illawarra Shoalhaven Local Health Districts, and Sydney Children's Hospital, all in NSW, Australia. These districts cover a geographic area of 6,331 square kilometres and have an estimated population of 1.17 million, extending from central Sydney to three hours' drive south (New South Wales Health, 2010). Comparable adult metrics were available for analysis in five hospitals, comprising 1900 beds, as shown in Figure 5.1. The remaining hospitals were not included in the study for the following reasons: small size, ASP implementation outside of study period, specialist (i.e. obstetrics, paediatrics) or subacute admissions (Figure 5.1). Those attributes would not allow comparison of outcomes such as antimicrobial use, LOS or HCA-CDI. The specialist paediatric hospital contributed to the development of guidelines for paediatric services within the other hospitals. Hospitals

shared AMS strategies, including a centrally deployed CDSS (Guidance MS®, Melbourne Health) (Guidance Group, 2013), educational material and similar antimicrobial formulary restrictions. Further information on case complexity and case mix of the included study hospitals is provided in Table 5.1.

5.4.2 Intervention

An ITS study was conducted combining data from five acute hospitals. The intervention point for the ASP was defined as the go-live date of the CDSS with concurrent dissemination of standardised antimicrobial prescribing guidelines at each site (May-July 2012). This occurred in the setting of a 6-month lead-in period of prior education and antimicrobial guideline development (Figure 5.1). The fully modifiable CDSS, Guidance MS® is an intranet browser-based CDSS that guides prescribers on appropriate use and generates approvals for antimicrobials (Guidance Group, 2013). Antimicrobial restriction (a key component of our ASP) within the CDSS is determined on the basis of spectrum of action, potential toxicity or cost (Guidance Group, 2013). Implementation of the CDSS used project methodology (PRINCE2®, ILX Group, Mulgrave, Victoria, Australia) and was overseen by a multidisciplinary committee of medical, pharmacy, information technology (IT), and executive staff. The committee met monthly via teleconference and collaborated closely throughout the project implementation period (May 2011 - May 2012). This period was critical to optimise organisational readiness for implementation of a CDSS-supported ASP (Duguid and Cruickshank, 2010).

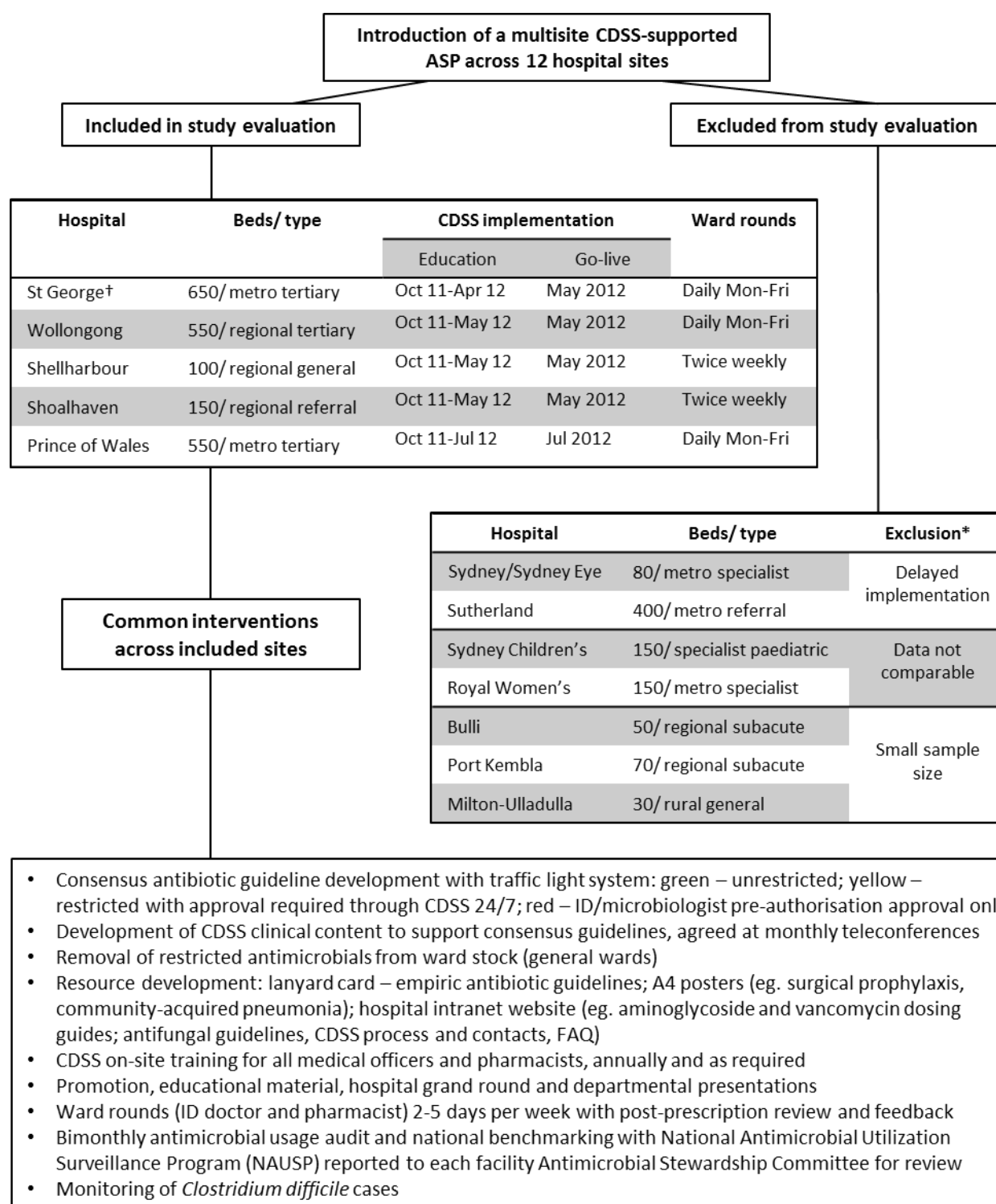


Figure 5.1: Population, clinical setting, nature and timing of interventions

†Phone-based AMS with formulary restriction implemented Nov 2008

Figure 5.1 (cont): *Exclusions: delayed implementation, hospital sites had delayed recruitment of specialist staff and inadequate reporting of antimicrobial benchmarking data; data not comparable, specialist children's and women's hospitals with non-comparable patient and case mix; small sample size, antimicrobial use and cost data not reported to the National Antimicrobial Utilisation Surveillance Program (NAUSP); CDI, LOS and mortality data not analysed due to small sample size and high proportion of sub-acute admissions

Antimicrobial guidelines were based on national guidelines (Antibiotic Expert Group, 2010), then standardised across the hospitals and incorporated into the CDSS. The development of guidelines, educational content and decision support was shared by adult and paediatric ID physicians and AMS pharmacists. This allowed for a standardised intervention that was tailored to hospital size and level of acuity (Figure 5.1), thereby reducing individual hospital workload, allowing access to clinical expertise at smaller sites and ensuring timely consensus on CDSS clinical content. Staffing (ID physicians, pharmacists and microbiologists) varied across the hospital sites, so intranet-based guidelines and an antibiotic advice hotline were used to promote access to program resources. Standardised bimonthly nationally benchmarked antimicrobial usage audits were reported to respective hospital AMS committees (South Australian Health, 2016). Prior to the study, AMS activities were restricted to phone-based advice, formal ID consults, selective antimicrobial sensitivity reporting, restriction of antifungals and reserve antibacterials (e.g. linezolid, tigecycline, colistin and daptomycin), and a phone-based approval system at one study hospital (Figure 5.1).

Study investigators classified the most commonly used antimicrobial classes into two categories, either targeted for increased or decreased use. Categorisation was based on the

following factors: local AMR patterns, local use compared with benchmarked hospitals (South Australian Health, 2016), risk of HCA-CDI and other side effects, compliance with antibiotic guidelines (Antibiotic Expert Group, 2010), and cost. Antimicrobials targeted for increased use were benzylpenicillin, doxycycline and aminopenicillins, whereas antimicrobials targeted for decreased use were third generation cephalosporins, macrolides, anti-pseudomonal beta-lactam/beta-lactamase inhibitor combinations, fluoroquinolones, and carbapenems. Additional antimicrobials were targeted for increased use in some settings, but decreased use in others. For example, local quality audits identified underdosing in surgical prophylaxis, but unnecessarily long duration of therapy in other settings such as cellulitis (data not shown). Such antimicrobials (i.e. first generation cephalosporins, flucloxacillin, aminoglycosides, and vancomycin) were only included in the overall antimicrobial use analysis.

The infection control policies related to *Clostridium difficile* and hand hygiene were not subject to any major changes during the study period. Infection control measures recommended by local policies included: isolation in single rooms; use of disposable gowns and gloves; hand hygiene with alcohol-based hand rub and/or soap and water; and terminal cleaning with chlorine-based disinfectant. Diagnostic testing methods for *Clostridium difficile* were comparable across the health districts' three main laboratories from May 2010, and included first line testing with targeted GDH antigen and toxins A and B (e.g. C. Diff Quik Chek Complete®, Techlab, Blacksburg, VA, USA). Discordant results occasioned the use of a PCR (e.g. GeneXpert®, Cepheid, Sunnyvale, CA, USA) test. All diarrhoeal stools were subjected to testing from December 2010 (seven months after the beginning of the pre-intervention period). A subset of the CDI data has been

published previously in a different context (Bond et al., 2016). Those data have been included here to allow comparison in the multisite setting.

5.4.3 Outcomes

The effect of the intervention was assessed by: (1) change in antimicrobials targeted for increased use (benzylpenicillin, doxycycline and aminopenicillins) expressed as DDDs per 1000 OBDs; (2) change in antimicrobials targeted for decreased use (third generation cephalosporins, macrolides, anti-pseudomonal beta-lactam/beta-lactamase inhibitor combinations, fluoroquinolones, and carbapenems; DDDs/1000 OBDs) (World Health Organisation, 2017); (3) change in total monthly antimicrobial costs (AU\$). High cost antifungals (liposomal amphotericin, anidulafungin, caspofungin, posaconazole, and voriconazole) were analysed separately to the main antimicrobial group due to small variations in use accounting for large cost variations; (4) change in HCA-CDI rates, defined as a positive laboratory test for toxigenic *Clostridium difficile* plus diarrhoea onset greater than 48 hours after hospital admission (HCA-CDI cases per 10,000 OBDs) (Australian Council on Healthcare Standards, 2014); and (5) change in LOS and in-hospital SMR for respiratory tract infections, cellulitis, kidney and urinary tract infections, and septicaemia, compared with background figures for all conditions (infectious and non-infectious combined). Confounders for each of the above measures were also investigated and reported where appropriate. Those included infection outbreaks, updated guidelines, changes to drug acquisition costs and administrative changes.

5.4.4 Data sources

Adult inpatient data were included from May 2010 to July 2014. Antimicrobial use and acquisition cost data were obtained from pharmacy dispensing software, iPharmacy® Versions 5.5 and 5.6 (CSC, Sydney, Australia). Antimicrobial use data were processed by NAUSP (South Australian Health, 2016) using WHO classifications. OBD data were sourced from the hospitals' performance units. HCA-CDI numbers were provided by the infection control teams in line with standardised surveillance and reporting (Australian Council on Healthcare Standards, 2014). LOS (using Australian refined DRGs) (Australian Institute of Health and Welfare, 2016) and SMRs (using principal diagnosis codes, based on International Classification of Diseases, 10th revision, Australian modification) (Australian Institute of Health and Welfare, 2016) were provided by the performance units for the following key infections: respiratory infections/inflammations (predominantly pneumonia), cellulitis, and kidney and urinary tract infections. Those were the commonest treatment indications for antimicrobials in the 2014 Australian NAPS (Australian Commission on Safety and Quality in Health Care, 2015). Septicaemia was also included due to its high mortality (Gauer, 2013). LOS and SMRs were compared for the time periods 1 July 2010 – 30 June 2012 and 1 July 2012 – 30 June 2014, as only data aligned with Australian financial years was available. Analysis of overall LOS excluded day case haemodialysis admissions. Comparative case complexity and case mix of the study hospitals was reported using National Weighted Activity Units (NWAUs) (National Health Funding Pool, 2016) and DRGs (Table 5.1) (Australian Institute of Health and Welfare, 2016).

5.4.5 Statistical analyses

ITS analysis with segmented linear regression was used to examine the impact of the intervention on monthly antimicrobial use, costs and HCA-CDI, estimating the immediate effects of the intervention and changes in trend (Linden, 2015). To account for seasonal variations, 24 time points one month apart were used pre- and post-intervention (Ansari et al., 2003). To allow for statistical analysis of two years pre- and two years post-intervention, the intervention point (go-live date of CDSS-supported ASP) was aligned for the five hospitals, with individual hospital data provided in Table 5.5 and Table 5.6. Definitions for ITS were: (1) initial level, model-predicted level (antimicrobial use, cost, HCA-CDI) 24 months pre-intervention; (2) initial trend, model-predicted monthly trend pre-intervention; (3) change in level (immediate effect), model-predicted difference between the level at the end of the pre-intervention period and commencement of the post-intervention period (Cairns et al., 2013); (4) change in trend, model-predicted difference between initial (pre-intervention) monthly trend and post-intervention trend. Autocorrelation using Newey-West approximation for standard errors was investigated and an appropriate lag was used when necessary, in order to assess for similarity between observations (Linden, 2015). LOS was assessed using Mann-Whitney U-test. A logistic regression model was used to calculate the number of expected deaths using: age; sex; admission type (emergency or acute); admission source (acute transfer or other); principal diagnosis, and Charlson Comorbidity Index (0, 1-2, or 3+) (Charlson et al., 1987). Additional variables used in the expected deaths analysis related to vascular surgery, cardiac surgery, neurosurgery, trauma and transplant. Those figures were then used to calculate infection-related and total SMR (actual deaths/expected deaths). SMRs (pre-

and post-intervention) were expressed with 95% confidence intervals (CIs). Statistical significance was considered $p < 0.05$. Statistical analyses were performed using Stata® Statistical Software: Release 14 (Statacorp 2015; College Station, TX, USA).

5.4.6 Ethics

Ethics approval was obtained from the districts' Human Research Ethics Committees, approval number HE13/137 (Appendix E).

5.5 Results

5.5.1 Antimicrobial use

Following the intervention, a rise in antimicrobials targeted for increased use of 70 DDDs/1000 OBDs (+32%; $p < 0.01$) was observed, followed by a decline in trend of 3.5 DDDs/1000 OBDs per month ($p < 0.01$). A concomitant reduction in antimicrobials targeted for decreased use of 58 DDDs/1000 OBDs (-23%; $p < 0.01$) was observed, followed by a rise in trend of 3.4 DDDs/1000 OBDs per month ($p < 0.01$; Figure 5.2). No significant change in level or trend was observed for overall antimicrobial use. There was a national shortage of benzylpenicillin in 2010-11; ampicillin was recommended as an alternative for most benzylpenicillin indications during this time. The national antimicrobial guidelines (Antibiotic Expert Group, 2010; Antibiotic Expert Groups, 2014) were updated in 2010 and again in 2014.

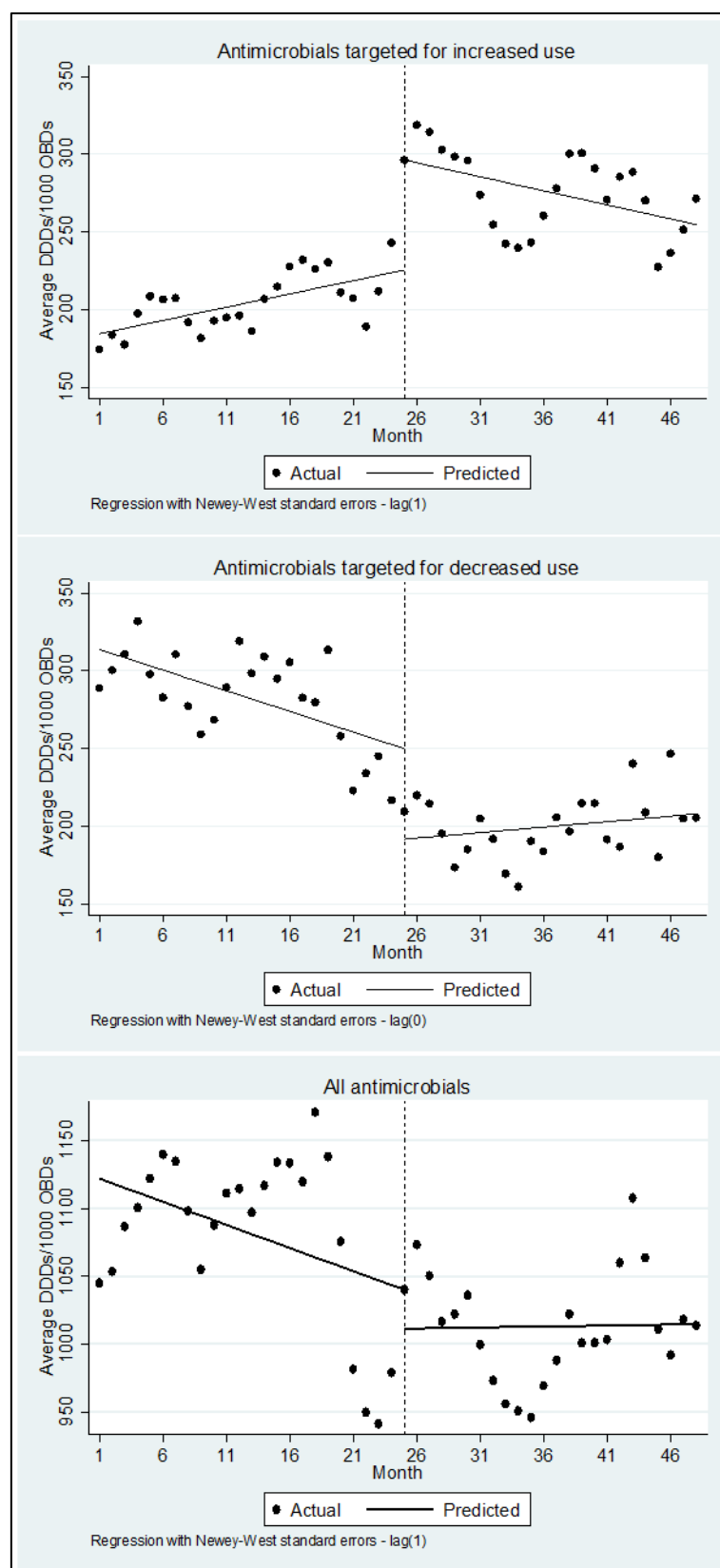


Figure 5.2: Impact of the AMS intervention on antimicrobial use

Figure 5.2 (cont): Abbreviations: DDDs, defined daily doses; OBDs, occupied bed days

Targeted for increased use: benzylpenicillin, doxycycline, aminopenicillins (amoxycillin and ampicillin); targeted for decreased use: third generation cephalosporins (ceftriaxone, cefotaxime), macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin), anti-pseudomonal penicillins (piperacillin/tazobactam, ticarcillin/clavulanic acid), fluoroquinolones (ciprofloxacin, moxifloxacin, norfloxacin); carbapenems (ertapenem, doripenem, imipenem/cilastatin, meropenem) total antimicrobials, all antimicrobials excluding antifungals and antivirals; vertical line is introduction of a CDSS-supported ASP, including antimicrobial restriction and education.

5.5.2 Antimicrobial costs

There was a significant reduction in total monthly antimicrobial costs of AU\$64,551 (-17%; $p < 0.01$) post-intervention, followed by an increase in trend of AU\$7,273 per month ($p < 0.01$; Table 5.3). This corresponded to a reduction of AU\$1.70/OBD post-intervention (-20%; $p < 0.01$), with a subsequent increase in trend of AU\$0.26/OBD per month ($p < 0.01$). High cost antifungals demonstrated an immediate cost reduction ($p < 0.01$), with no significant increase in trend. Some changes in acquisition costs were noted prior to the intervention, most notably a reduction in meropenem acquisition costs in mid-2011.

5.5.3 HCA-CDI rates

HCA-CDI rates were increasing pre-intervention from 2.8 to 6.2 cases/10,000 OBDs per month ($p < 0.01$). A reduction was demonstrated post-intervention (-1.2 cases/10,000 OBDs/month, $p = 0.15$), followed by a decrease in trend ($p < 0.01$; Table 5.3; Figure 5.3).

There were no systemic changes to hand hygiene and cleaning policies during the study period. The rate of hand hygiene compliance had increased across facilities following

national initiatives prior to 2009. There were no notable HCA-CDI outbreaks from 2010-2014.

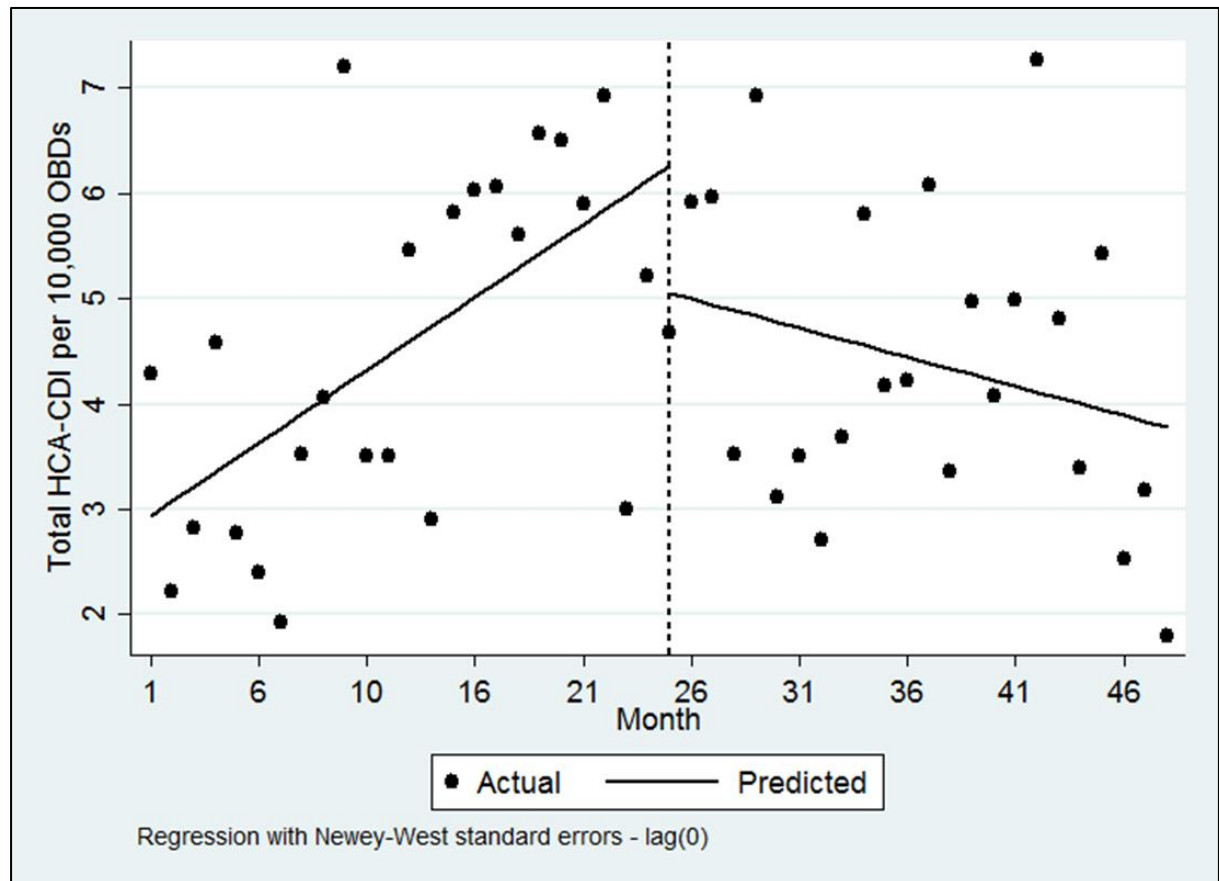


Figure 5.3: Impact of the AMS intervention on HCA-CDI rates

Abbreviations: HCA-CDI, healthcare associated *Clostridium difficile* infection

Two years of monthly HCA-CDI rates pre- and post-intervention; vertical line is introduction of a CDSS-supported ASP.

5.5.4 LOS

Median LOS was reduced for respiratory infections (4.8 to 4.3 days, $p < 0.01$), cellulitis (3.2 to 2.9 days, $p < 0.01$), urinary and kidney infections (3.3 to 2.9 days, $p < 0.01$), and

septicaemia (6.8 to 6.1 days, $p<0.01$; Table 5.4). Over the same time period, median LOS for all hospital admissions also decreased from 2.1 to 1.9 days ($p<0.01$).

5.5.5 In-hospital SMR

SMRs decreased for respiratory infections (1.10 [95%CI 1.01-1.20] to 0.75 [0.68-0.82] observed/expected deaths), urinary and kidney infections (0.78 [0.52-1.10] to 0.63 [0.42-0.91]), and septicaemia (1.25 [1.12-1.38] to 0.80 [0.72-0.89]). Reductions in those infection-related SMRs were in line with the reduction in background SMR (1.19 [1.15-1.23] to 0.90 [0.87-0.93]; Table 5.4). A small increase was observed for cellulitis (0.55 [0.28-0.95] to 0.66 [0.38-1.05]).

5.6 Discussion

To our knowledge, this is the first study to evaluate implementation of a multisite ASP supported by a centrally deployed CDSS. We found improvements in antimicrobial use, demonstrated by changes in antimicrobials targeted for increased and decreased use. There were significant reductions in antimicrobial costs and HCA-CDI rates. Safety of the intervention was supported by decreased or unchanged LOS and SMRs for key infections during the study period. The long-term impact of the intervention on antimicrobial use and cost diminished over time, which suggests that ongoing program reinforcement and targeted interventions may be required to alleviate “AMS fatigue”. Changes in overall antimicrobial use prior to the main intervention probably resulted from an intensive education campaign to optimise antimicrobial use across the hospitals, with

heightened awareness of the impending change among clinicians. The importance of readiness assessments prior to implementation was recognised, along with shared interventions across the study hospitals. Those included AMS ward rounds with post-prescription review and feedback, consensus guidelines, departmental education, and antimicrobial restriction.

Some studies have evaluated ASPs across multiple hospital sites (Ostrowsky et al., 2014; Antoine et al., 2006; Schuts et al., 2016) and the utility of an individual site CDSS for improvement in antimicrobial prescribing (Cairns et al., 2013; Kaushal et al., 2003; Buising et al., 2008; Thursky, 2006); however, the combination of these two approaches is novel. Furthermore, this collaborative ASP was applied to non-metropolitan settings with an established structure of support from a larger hospital. Pooling data across five hospitals enhanced the potential to identify effects of the ASP. Few randomised studies have been conducted to determine the effect of ASPs (Davey et al., 2013; Schuts et al., 2016). Our study used interrupted time series analysis, which is considered an alternative pragmatic approach with strong quasi-experimental design (Fowler et al., 2007). Comparison with control hospitals would have strengthened the study design; however, there were none available in the health districts due to widespread implementation of the ASP.

Our study demonstrates that shared knowledge and expertise can be used to effectively implement an ASP across multiple hospital sites spanning a wide geographic area. The economies of scale enjoyed by the multisite approach allowed for collective interventions to be employed with reduced workload at individual hospital sites. Multisite

implementation also alleviated some of the potential disadvantages of the CDSS, such as resources required for implementation and maintenance (Barlam et al., 2016). An additional benefit of extensive multisite intervention was consistency in antimicrobial prescribing guidelines, facilitating the training of medical officers rotating through the facilities within the districts' different hospitals. A consistent, multisite approach was also anticipated to enhance prescriber confidence and facilitate the quality improvement culture necessary to effect longer term improvements in antimicrobial prescribing (Broom et al., 2014; Charani et al., 2011).

ASPs are a key element of the approach to reducing HCA-CDI (Leffler and Lamont, 2015). Importantly, our intervention was associated with a reduction in HCA-CDI rates, as well as a decrease in trend that persisted over time. This occurred in the context of increasing community CDI rates (Slimings et al., 2014).

The specialist paediatric hospital and paediatric wards from study sites were not included in this analysis. Non-comparability of standard adult metrics such as DDDs results in difficulty benchmarking antimicrobial use in children (Porta et al., 2012). HCA-CDI cannot easily be assessed in the paediatric population due to asymptomatic carriage in infants and lower rates of symptomatic CDI in children (Sammons et al., 2013). Although quantitative paediatric data were not included in this study, paediatric antimicrobial guideline and CDSS development were important for multisite ASP implementation across the network of small rural to large metropolitan hospitals.

Maintaining cost effectiveness is of concern to administrators (McGowan, 2012). Placing drug costs as the primary measure of cost analysis does not take into account changes in acquisition costs (e.g. when drugs come off patent). In addition, the most appropriate antimicrobial is not necessarily the lowest in price. Identifying other methods of cost benefit analysis is justified, such as the impact of healthcare associated infections, and the increased cost of treating resistant organisms (Goff, 2011). Some cost savings were attributed to reductions in drug acquisition costs, such as for meropenem in 2011. Paradoxically, the intervention was associated with increased drug costs in some instances. Benzylpenicillin, targeted for increased use, had a daily cost at usual dosing (1.2g intravenously 6 hourly) of AU\$25, compared with ceftriaxone (targeted for decreased use; AU\$1.30 for 1g intravenously daily). In addition, the post-intervention cost increase may have been driven by high cost antifungal use where treatment of a small number of patients may result in a significant increase in drug costs. Building works at some of the sites, leading to increased prophylaxis and treatment of invasive fungal infections, may have led to this increase. However, antifungals were not a main target of the collaborative ASP as they were already highly restricted prior to the intervention. Costs of the intervention were not analysed as part of this study; there were costs associated with purchasing the CDSS, and additional pharmacy and ID resources in supporting the ASPs.

There were some other limitations to this study. Antimicrobial use patterns may also have been affected by unforeseen drug shortages and changes to infection control practices. There were no systematic changes to the infection control policies across the districts during the study period, and no recognised outbreaks of CDI occurred during this time.

Some measures were not included due to a lack of comparable pre- and post-intervention data across sites; these included the impact of antimicrobial stewardship ward rounds, point prevalence survey results and AMR patterns. Antimicrobials analysed included only those targeted for increased (e.g. benzylpenicillin) or decreased (e.g. ceftriaxone) use. Not all antimicrobial classes were reported individually, such as glycopeptides (e.g. vancomycin) and first generation cephalosporins (e.g. cephalazolin, cephalexin). Although often targeted in ASPs, based on national guidelines (Antibiotic Expert Group, 2010) there were instances where these classes were targeted for either increased or decreased use. As such, it was not clear whether the ASP would result in a change to use. Reserve antibacterial agents such as linezolid and daptomycin were already highly restricted prior to the intervention, requiring prior physician approval before use.

The effect of the intervention was not uniform across the sites. Reasons for this variability may have included differences in maturity of existing antimicrobial stewardship initiatives prior to the introduction of the CDSS, disparate levels of acuity, and variable patterns of resistance. Pre-existing AMS initiatives at all sites consisted of selective microbiology reporting, limited ID and microbiology phone support, and some departmental education, with one site additionally using a phone-based approval system (Figure 5.1). Variation in case complexity and case mix between study hospitals (Table 5.1) may have justified some differences in antimicrobial use. Additionally, seasonal variation was evident in the antimicrobial use patterns. Those confounders may have been alleviated by using combined antimicrobial use data with sufficient pre- and post-intervention time points for the ITS analysis. Data on antimicrobial use, cost and HCA-CDI data could not be aligned perfectly in time with LOS and mortality data due to report

limitations; however, the maximum lag (for one hospital) was only 6 weeks over a 48 month period. Infection-related and overall LOS decreased after the intervention, which may have been due to increased use of hospital in the home services. There may have been potential confounders, such as changes to funding and hospital admission models that affected LOS and SMR during the intervention which were difficult to quantify. However, LOS and SMR were included as important balancing measures as they could potentially be negatively impacted by changed patterns of antimicrobial use. Statewide programs were also introduced by the NSW Clinical Excellence Commission through 2010-2014 to improve management of deteriorating patients (*Between the Flags* program) and recognition and management of sepsis (*Sepsis Kills* program) (Clinical Excellence Commission, 2016). Those initiatives potentially contributed to the improvements in LOS and SMR in the post-intervention period.

We anticipate that our findings would be generalisable to healthcare facilities with potential for utilising shared resources, such as those with existing professional or political networks. Additional studies using prospective methodological approaches in different settings would help to validate our results.

5.6.1 Conclusions

Implementation of a multisite ASP supported by a centrally deployed CDSS was associated with significant changes to targeted antimicrobial use, containment of antimicrobial expenditure and reduction in HCA-CDI, without obvious adverse effects. Ongoing targeted interventions involving education and behaviour change are required to sustain the benefits of ASPs on hospital antimicrobial use.

5.6.2 Acknowledgements

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5.8 Tables

Table 5.1: Case complexity and case mix of study hospitals for the Australian financial year 2013 – 2014

Hospital	Total acute episodes	Total acute NWAU(16)	Average NWAU(16) per acute episode	Top five DRGs by volume
Prince of Wales	32,699	49,513	1.51	Chest pain; cellulitis; other digestive system diagnosis; respiratory infection/ inflammation; injuries
Shellharbour	8,213	11,246	1.37	Respiratory infection/ inflammation; schizophrenia disorders; chronic obstructive airway disease; hernia procedures; personality disorder and acute reactions
Shoalhaven	10,970	12,678	1.16	Uncomplicated neonatal admission; vaginal delivery; respiratory infection/ inflammation; chronic obstructive airway disease; caesarean delivery
St George	39,234	57,138	1.46	Uncomplicated neonatal admission; vaginal delivery; chest pain; respiratory infection/ inflammation; oesophagitis and gastroenteritis
Wollongong	36,951	50,813	1.38	Uncomplicated neonatal admission; vaginal delivery; respiratory infection/ inflammation; cellulitis; caesarean delivery

Australian financial year, 1 July 2013 to 30 June 2014; total acute episodes excludes haemodialysis, due to a large number of episodes without significant antimicrobial use; NWAU(16), National weighted activity unit (2015/16), a measure of comparing and valuing each public hospital service, to determine the overall complexity and relative resource payment for services funded on an activity basis. DRGs, Australian-refined diagnosis related group.

Table 5.2: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use

	Pre-intervention							Post-intervention							
Antimicrobial	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Combined targeted for increased use	182 ^a	170	195	1.7 ^a	0.7	2.8	<0.01	71 ^a	43	98	<0.01	-3.5 ^a	-5.3	-1.7	<0.01
Combined targeted for decreased use	316	298	334	-2.6	-4.1	-1.2	<0.01	-58	-87	-29	<0.01	3.4	1.4	5.3	<0.01
Total antimicrobial use	1125 ^a	1033	1184	-3.4 ^a	-8.9	2.1	0.22	-29 ^a	-129	71	0.57	3.55 ^a	-2.6	9.7	0.25

Antimicrobial use (level) expressed as average defined daily doses/1000 occupied bed days for five hospitals, as reported to NAUSP; trends: positive value represents increase, negative value represents decrease; 95% confidence intervals expressed as LCI (lower confidence interval) and UCI (upper confidence interval); ^aadjusted for first order autocorrelation; targeted for increased use: benzylpenicillin, doxycycline, aminopenicillins (amoxycillin, ampicillin); targeted for decreased use: third generation cephalosporins (ceftazidime, cefotaxime, ceftriaxone); macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin); anti-pseudomonal penicillins (piperacillin/tazobactam, ticarcillin/clavulanic acid); fluoroquinolones (ciprofloxacin, moxifloxacin, norfloxacin); carbapenems (meropenem, ertapenem, doripenem, imipenem/cilastatin); individual hospital data provided in Table 5.5.

Table 5.3: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare associated *Clostridium difficile* infection

	Pre-intervention							Post-intervention							
Variable	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total ^b costs (\$AU)	463375 ^a	417101	509649	-3196 ^a	-5759	-633	0.02	-64551 ^a	-106056	-23044	<0.01	7273 ^a	3899	10649	<0.01
Costs per OBD (\$AU)	9.9	8.7	11.1	-0.07	-0.14	-0.01	<0.01	-1.7	-2.6	-0.8	<0.01	0.26	0.18	0.34	<0.01
Antifungal ^c costs (\$AU)	92575	67721	117429	2021	376	3666	0.02	-50270	-86637	-13903	<0.01	1117	-1504	3738	0.40
HCA-CDI per 10,000 OBDs	2.8	1.7	3.9	0.14	0.06	0.22	<0.01	-1.2	-2.8	0.4	0.15	-0.2	-0.3	0.1	<0.01

Abbreviations: OBD, occupied bed day; \$AU, Australian dollars; HCA CDI, healthcare associated *Clostridium difficile* infection.

^aadjusted for first order autocorrelation; trends: positive value represents increase, negative value represents decrease; ^bantibacterial, antifungal, antiviral ^chigh cost antifungals: liposomal amphotericin, anidulafungin, caspofungin, posaconazole, voriconazole; individual hospital data provided in **Table 5.6**.

Table 5.4: Length of stay and standardised mortality ratio by clinical infection group

Outcome measure	Length of stay					Standardised mortality ratio			
	July 10 – June 12		July 12 – June 14		p value	July 10 – June 12		July 12 – June 14	
	Episodes	Median LOS (IQR), days	Episodes	Median LOS (IQR), days		Standardised mortality ratio (95% CI)	Actual/expected deaths	Standardised mortality ratio (95% CI)	Actual/expected deaths
Respiratory infections	5,489	4.8 (2.8-7.8)	5640	4.3 (2.5-7.1)	<0.01	1.10 (1.01-1.20)	534/485	0.75 (0.68-0.82)	436/584
Cellulitis	3,696	3.2 (1.6-5.8)	3757	2.9 (1.2-5.0)	<0.01	0.55 (0.28-0.95)	12/22	0.66 (0.38-1.05)	17/26
Urinary and kidney infections	4,323	3.3 (1.2-5.2)	4364	2.9 (1.0-5.2)	<0.01	0.78 (0.52-1.10)	30/39	0.63 (0.42-0.91)	29/46
Septicaemia	1,610	6.8 (4.0-11.7)	2441	6.1 (3.5-10.9)	<0.01	1.25 (1.12-1.38)	350/281	0.80 (0.72-0.89)	359/450
Overall	224,021	2.1 (0.6-5.6)	242,383	1.9 (0.5-5.0)	<0.01	1.19 (1.15-1.23)	3795/3193	0.90 (0.87-0.93)	3647/4063

Abbreviations: LOS, length of stay; IQR, interquartile range; CI, confidence interval

Respiratory infections/inflammations, code E62; cellulitis, code J64; urinary and kidney infections, code, L63; septicaemia, code T60; overall LOS excludes haemodialysis day admissions. Codes for LOS used Australian refined diagnosis related group definitions; codes for SMR used principal diagnosis codes, based on International Classification of Diseases, 10th revision, Australian modification.

Table 5.5a: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, by hospital

Prince of Wales Hospital

		Pre-intervention							Post-intervention							
	Antimicrobial	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	19 ^a	11	28	0.5	-0.1	1.2	0.1	4.9	-8.6	18.4	0.5	-0.3	-1.2	0.6	0.5
	Doxycycline	10 ^a	5	15	2	1.5	2.5	<0.01	4.4	-6.8	15.6	0.4	-1.8	-2.6	-0.9	<0.01
	Aminopenicillins	146 ^a	129	163	-0.8	-1.8	0.3	0.15	3.0	9.3	47.5	<0.01	0.4	-1.0	1.7	0.6
	Combined	175 ^a	148	202	1.78	0.1	3.4	0.04	38	14.0	61.4	<0.01	-1.68	-4.1	0.68	0.15
Targeted for decreased use	3 rd gen cephalosporins	75 ^a	68	83	-0.6	-1.0	-0.3	<0.01	1.7	-4.7	8.2	0.6	0.8	0.2	1.5	0.01
	Macrolides	95 ^a	80	111	-0.6	-1.6	0.4	0.2	-13	-35	8.8	0.2	0.4	-1.2	1.9	0.6
	Anti-pseudomonal penicillins	28 ^a	23	33	0.7	0.4	1.0	<0.01	-4.9	-13	3.3	0.24	-0.67	-1.1	-0.2	<0.01
	Fluoroquinolones	72	62	81	-1.8	-1.4	-0.2	0.01	-0.2	-12	12	0.98	0.1	-1	1.1	0.87
	Carbapenems	25	17	34	0.4	-0.2	1.0	0.2	3.4	-7.4	14	0.5	-0.5	-1.3	0.3	0.25
	Combined	296	270	322	-0.9	-2.7	0.8	0.3	-13	-47	21	0.4	0.1	-2.4	2.5	0.9
	Total antimicrobial use	1109 ^a	1078	1140	0.8	-3.2	1.6	0.5	69	20	119	<0.01	3.6	-0.8	8.1	0.1

Antimicrobial use (level) expressed as average defined daily doses/1000 occupied bed days, as reported to NAUSP; 95% confidence intervals expressed as LCI (lower

confidence interval) and UCI (upper confidence interval); trends: positive value represents increase, negative value represents decrease.

^aadjusted for first order autocorrelation; aminopenicillins, amoxycillin, ampicillin; third generation cephalosporins, ceftriaxone and cefotaxime; macrolides, azithromycin,

clarithromycin, roxithromycin, erythromycin; anti-pseudomonal penicillins, piperacillin-tazobactam and ticarcillin-clavulanic acid; fluoroquinolones, ciprofloxacin,

moxifloxacin and norfloxacin; carbapenems, ertapenem, doripenem, imipenem/cilastatin, meropenem.

Table 5.5b: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, by hospital

Shellharbour Hospital

		Pre-intervention							Post-intervention							
	Antimicrobial	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	13	-1.1	26	0.17	-0.8	1.2	0.7	35	17	53	<0.01	-1.4	-2.7	-0.1	0.03
	Doxycycline	22 ^a	8	35	5.2	3.9	6.5	<0.01	74	33	115	<0.01	-7	-10	-4	<0.01
	Aminopenicillins	98 ^a	80	117	-0.2	-1.6	1.2	0.75	53	25	81	<0.01	-1.3	-2.9	0.3	0.1
	Combined	132 ^a	96	168	5.2	2.5	7.8	<0.01	162	99	226	<0.01	-9.9	-14.2	-5.6	<0.01
Targeted for decreased use	3 rd gen cephalosporins	94	78	110	-1.2	-2.9	0.6	0.19	-29	-59	2	0.06	2.1	0.3	3.9	0.02
	Macrolides	295	259	331	-6.1	-8.7	-3.4	<0.01	-65	-127	-3.4	0.04	5.7	2.9	8.4	<0.01
	Anti-pseudomonal penicillins	17	13	21	0.03	-0.3	0.3	0.88	-8	-15	-1	0.02	0.25	-0.2	0.7	0.28
	Fluoroquinolones	55	35	75	-0.001	-1.6	1.6	1	-30	-58	-1	0.04	0.7	-1.3	2.6	0.5
	Carbapenems	5	2	7	-0.05	-0.2	0.1	0.57	-1.5	-5	2	0.41	0.2	-0.1	0.5	0.18
	Combined	466	400	530	-7.3	-13	-1.2	0.02	-133	-245	-22	0.02	8.9	1.9	16	0.01
	Total antimicrobial use	1295 ^a	1191	1399	-8	-18	3	0.14	-42	-252	167	0.7	6.7	-5.3	18	0.27

Table 5.5c: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, by hospital

Shoalhaven Hospital

		Pre-intervention							Post-intervention							
	Antimicrobial	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	36	22	49	0.03	-1.1	1.2	1	9	-13	31	0.8	-0.2	-1.5	1.1	0.7
	Doxycycline	108 ^a	71	143	0.4	-1.7	2.6	0.7	54	26	81	<0.01	-1.1	-3.5	1.3	0.4
	Aminopenicillins	202 ^a	190	214	-2.4	-3.3	-1.5	<0.01	19	-11	49	0.2	2.2	0.2	4.1	0.03
	Combined	344 ^a	302	387	-2.0	-4.4	0.5	0.12	82	32	131	<0.01	0.8	-3.0	4.6	0.68
Targeted for decreased use	3 rd gen cephalosporins	54	42	67	0.3	-0.5	1.0	0.5	-16	-27	-6	<0.01	-0.5	-1.4	0.4	0.24
	Macrolides	170	153	187	-3.2	-4.4	-1.9	<0.01	-40	-84	3	0.07	5.1	-0.3	11	0.06
	Anti-pseudomonal penicillins	21	16	26	-0.01	-0.3	0.3	0.97	-5	-12	1.7	0.14	0.63	-0.02	1.3	0.06
	Fluoroquinolones	66	57	75	-1	-1.7	-0.3	<0.01	-13	-30	3.4	0.12	0.85	-0.2	1.9	0.12
	Carbapenems	9 ^a	6	11	-0.2	-0.3	-0.01	0.04	-2	-6.5	2.5	0.37	0.4	0.1	0.8	0.02
	Combined	320	293	346	-4.1	-5.8	-2.3	<0.01	-77	-128	-27	<0.01	6.5	0.9	12	0.02
	Total antimicrobial use	1508 ^a	1391	1625	-15	-24	-7	<0.01	-104	-249	40	0.15	17	8	27	<0.01

Table 5.5d: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, by hospital

St George Hospital

		Pre-intervention							Post-intervention							
	Antimicrobial	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	20 ^a	14	27	0.7	0.2	1.2	<0.01	-16	-24	-7	<0.01	-0.1	-0.7	0.4	0.6
	Doxycycline	1.4 ^a	-2.9	5.6	1.1	0.84	1.43	<0.01	-0.1	-8.5	8.3	0.98	-1.0	-1.6	-0.5	<0.01
	Aminopenicillins	75 ^a	69	81	2.0	1.28	2.69	<0.01	8.1	-6.8	23.0	0.3	-3.8	-4.7	3.0	<0.01
	Combined	96 ^a	85	107	3.8	2.8	4.9	<0.01	-7.6	-27.8	12.6	0.45	-5.0	-6.3	-3.8	<0.01
Targeted for decreased use	3 rd gen cephalosporins	44	37	50	0.5	0	1.06	0.051	-4.0	-14	6.1	0.43	-0.9	-1.5	-0.3	<0.01
	Macrolides	80	68	90	0.9	-0.1	1.9	0.09	-6.4	-28	15	0.56	-2.0	-3.4	-0.7	<0.01
	Anti-pseudomonal penicillins	18 ^a	15	20	0.8	0.6	1.0	<0.01	-7	-12	-2	<0.01	-0.08	-0.4	0.2	0.6
	Fluoroquinolones	29 ^a	24	34	0.2	-0.1	0.5	0.13	-5	-9	-1	0.02	-0.1	-0.5	0.2	0.43
	Carbapenems	13 ^a	10	15	0.1	-0.02	0.3	0.09	3.2	-2.4	8.8	0.25	-0.1	-0.4	0.2	0.5
	Combined	183	165	202	2.5	0.8	4.3	<0.01	-19	-54	15	0.27	-3.3	-5.4	-1.2	<0.01
	Total antimicrobial use	633	590	676	14	11	18	<0.01	-43	-98	12	0.12	-17	-20	-13	<0.01

Table 5.5e: Impact of a CDSS-supported multisite ASP on monthly antimicrobial use, by hospital

Wollongong Hospital

		Pre-intervention							Post-intervention							
	Antimicrobial	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Targeted for increased use	Benzylpenicillin	20	15	26	-0.3	-0.7	0.06	0.1	18	11	25	<0.01	-0.05	-0.6	0.5	0.8
	Doxycycline	30 ^a	19	40	1.2	0.1	2.3	0.03	35	8	61	0.01	-2.5	-4	-1	<0.01
	Aminopenicillins	114 ^a	104	124	-1.2	-2.1	-0.3	0.01	27	11	44	<0.01	0.8	-0.3	1.9	0.15
	Combined	164 ^a	143	186	-0.3	-2.3	1.8	0.8	80	39	120	<0.01	-1.8	-4.4	0.8	0.18
Targeted for decreased use	3 rd gen cephalosporins	51	42	61	-0.3	-0.9	0.4	0.4	-8	-17	1	0.08	0.56	-0.2	1.3	0.12
	Macrolides	123	110	137	-1.9	-3.0	-0.9	<0.01	-13	-34	8.5	0.23	1.5	0.4	2.5	<0.01
	Anti-pseudomonal penicillins	49 ^a	41	58	-0.3	-0.9	0.2	0.24	-7	-15	1.5	0.1	0.7	0.05	1.3	0.04
	Fluoroquinolones	73	63	83	-1	-1.8	-0.3	<0.01	-16	-30	-4	0.01	1.3	0.5	2.1	<0.01
	Carbapenems	19 ^a	15	23	0.01	-0.2	0.2	0.87	-3	-10	3	0.3	0.6	0.2	1.0	<0.01
	Combined	316	283	349	-3.6	-6.0	-1.2	<0.01	-48	-88	-7	<0.01	4.6	1.8	7.4	<0.01
	Total antimicrobial use	1081 ^a	1008	1156	-7	-15	0.2	0.06	-22	-159	114	0.74	6.4	-1.8	14.6	0.12

Table 5.6a: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection

rates, by hospital

Prince of Wales Hospital

	Pre-intervention							Post-intervention							
Variable	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs (\$AU)	174984 ^a	135818	214149	-2006	-4201	188	0.07	-7440	-37329	22449	0.62	2853	297	5410	0.03
Total costs per OBD (\$AU)	12	10	14	-0.15	-0.3	-0.003	0.045	-1.5	-3.5	0.5	0.15	0.55	0.35	0.75	<0.01
Antifungal ^b costs (\$AU)	56110 ^a	-705	2803	87	-1218	1391	0.9	-13288	-34951	8375	0.22	1049	-705	2803	0.23
HCA CDI per 10000 OBDs (n)	5.5	3.6	7.5	0.08	-0.05	0.2	0.2	0.4	-3.2	4.0	0.8	-0.24	-0.5	-0.01	0.04

Abbreviations: OBD, occupied bed day; \$AU, Australian dollars; HCA CDI, healthcare associated *Clostridium difficile* infection.

^aadjusted for first order autocorrelation; ^bhigh cost antifungals, liposomal amphotericin, caspofungin, voriconazole, posaconazole, anidulafungin.

Table 5.6b: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection

rates, by hospital

Shellharbour Hospital

	Pre-intervention							Post-intervention							
Variable	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs (\$AU)	12274	10351	14196	-37	-196	123	0.65	-2708	-6074	657	0.11	36	-175	247	0.73
Total costs per OBD (\$AU)	4.3 ^a	3.5	5.0	-0.02	-0.08	0.05	0.6	-0.85	-2	0.3	0.15	0.05	-0.02	0.11	0.16
Antifungal ^b costs (\$AU)	-88	-129	31	51	-29	130	0.2	-1177	-2893	540	0.17	-49	129	31	0.22
HCA CDI per 10000 OBDs (n)	1.1	-1.2	3.4	0.1	-0.02	0.25	0.09	-2.5	-5.6	0.5	0.1	-0.1	-0.3	0.1	0.4

Table 5.6c: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection

rates, by hospital

Shoalhaven Hospital

	Pre-intervention							Post-intervention change							
Variable	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs (\$AU)	28629	21020	36238	-624	-1037	-210	<0.01	89	-4122	4299	0.97	639	201	1077	<0.01
Total costs per OBD (\$AU)	8.5	6.2	109	-0.2	-0.3	-0.1	<0.01	0.14	-1.1	1.4	0.83	0.24	0.1	0.4	<0.01
Antifungal ^b costs (\$AU)	4409 ^a	23	386	-213	-368	-58	<0.01	2225	404	4046	0.02	204	22.5	386	0.03
HCA CDI per 10000 OBDs (n)	1.7	-0.3	3.7	0.1	-0.04	0.3	0.14	-0.1	-3.6	3.4	0.95	-0.2	-0.4	0.1	0.17

Table 5.6d: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection

rates, by hospital

St George Hospital

	Pre-intervention							Post-intervention change							
Variable	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs (\$AU)	104693 ^a	84724	124662	1688	206	3170	0.03	-61611	-85528	-37694	<0.01	828	-873	2529	0.33
Total costs per OBD (\$AU)	7.1 ^a	5.95	8.33	0.19	0.02	0.22	0.02	-4.7	-6.5	-2.9	<0.01	0.1	-0.01	0.23	0.06
Antifungal ^b costs (\$AU)	11112	-6465	28689	1998	390	3606	0.02	-46943	-74954	-18932	<0.01	-300	-2011	1411	0.73
HCA CDI per 10000 OBDs (n)	4.1	1.9	6.3	0.2	0.07	0.36	<0.01	-1.9	-4.5	0.7	0.15	-0.4	-0.6	-0.2	<0.01

Table 5.6e: Impact of a CDSS-supported multisite ASP on monthly antimicrobial costs and healthcare-associated *Clostridium difficile* infection

rates, by hospital

Wollongong Hospital

	Pre-intervention							Post-intervention change							
Variable	Initial level	LCI	UCI	Initial trend	LCI	UCI	p value	Change in level	LCI	UCI	p value	Change in trend	LCI	UCI	p value
Total costs (\$AU)	142796	122788	162803	-2218	-3396	-1040	<0.01	7120	-19333	33573	0.6	2917	1138	4667	<0.01
Total costs per OBD (\$AU)	12.3	10.6	14.1	-0.2	-0.3	-0.1	<0.01	0.5	-1.6	2.6	0.6	0.27	0.12	0.41	<0.01
Antifungal ^b costs (\$AU)	21032	-1051	1476	98	-713	908	0.8	8912	-6418	24242	0.25	212	-1051	1476	0.74
HCA CDI per 10000 OBDs (n)	1.6	0.5	2.6	0.15	0.06	0.24	<0.01	-1.9	-4.1	0.33	0.09	-0.08	-0.21	0.06	0.25

6 Design and implementation of a novel web-based e-learning tool for education of health professionals on the antibiotic vancomycin

Article published in *Journal of Medical Internet Research* (2017).

Bond SE, Crowther SP, Adhikari S, Chubaty AJ, Yu P, Borchard JP, Boutlis CS, Yeo WW, and Miyakis S (2017). ‘Design and implementation of a novel web-based e-learning tool for education of health professionals on the antibiotic vancomycin’, *Journal of Medical Internet Research*, Mar 30; 19(3):e93.

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6.1 Summary statement

This chapter investigates a novel e-learning approach for education on antimicrobial use. The theme builds on the use of technology to enable multisite education as discussed in Chapter 5. The potential benefits of the e-learning approach include: applicability to rural and regional settings, availability on mobile devices, and targeting of multiple health professional groups. Qualitative feedback is also employed, a theme that was additionally reported in Chapters 3 and 4. Further comparative investigation into the impact of the e-learning tool is described in Chapter 7.

6.2 Abstract

6.2.1 Background

Traditional approaches to health professional education are being challenged by increased clinical demands and decreased available time. Web-based e-learning tools offer a convenient and effective method of delivering education, particularly across multiple health care facilities. However, the effectiveness of this model for health professional education needs to be explored in context.

6.2.2 Objectives

The aims of this study were to (1) determine health professionals' experience and knowledge of clinical use of vancomycin, an antibiotic used for treatment of serious infections caused by MRSA and (2) describe the design and implementation of a web-based e-learning tool created to improve knowledge in this area.

6.2.3 Methods

We conducted a study on the design and implementation of a video-enhanced, web-based e-learning tool between April 2014 and January 2016. A web-based survey was developed to determine prior experience and knowledge of clinical vancomycin use among nurses, doctors, and pharmacists. The Vancomycin Interactive (VI) involved a series of short video clips interspersed with interactive question and answer scenarios, where only the correct response allowed for progression to the next section. Dramatic tension and humor were used as tools to engage users. Health professionals' knowledge

of clinical vancomycin use was obtained from website data; qualitative participant feedback was also collected.

6.2.4 Results

From the 577 knowledge survey responses, pharmacists (N=70) answered the greatest number of questions correctly (median score 4/5), followed by doctors (N=271; 3/5) and nurses (n=236; 2/5; $p<0.001$). Survey questions on target trough concentration range (75%; 433/577) and rate of administration (65%; 375/577) were answered most correctly, followed by timing of first level (49%; 283/577), maintenance dose (42%; 242/577), and loading dose (38%; 219/577). Self-reported “very” and “reasonably” experienced health professionals were also more likely to achieve correct responses.

The VI was completed by 163 participants during the study period. The rate of correctly answered VI questions on first attempt was 65% for nurses (N=63), 68% for doctors (N=86), and 82% for pharmacists (N=14; $p<0.001$), reflecting a similar pattern to that of the knowledge survey. Knowledge gaps were identified for loading dose (39% correct on first attempt; 64/163), timing of first trough level (50%; 82/163), and subsequent trough levels (48%; 78/163). Of the 163 participants, we received qualitative user feedback from 51 participants following completion of the VI. Feedback was predominantly positive with themes of “entertaining,” “engaging,” and “fun” identified; however, there were some technical issues identified relating to accessibility from different operating systems and browsers.

6.2.5 Conclusions

A novel web-based e-learning tool with interactive video content was successfully developed combining game design principles and humor to improve user engagement. Knowledge gaps were identified for different health professionals that allowed for targeting of future education strategies. The VI provides an innovative model for delivering web-based education to busy health professionals in different locations.

6.2.6 Keywords

Nursing education; pharmacy education; medical education; continuing education; vancomycin; survey methods; anti-bacterial agents.

6.3 Introduction

6.3.1 Internet-based learning

The development of IBL for healthcare professionals has increased in recent years (Liu et al., 2016). One reason for advancement of IBL is the existence of barriers associated with implementation of face-to-face health professional education, including increased clinical demands and decreased available time (Cook et al., 2010). These barriers become more evident where education is required across multiple facilities that are separated by long distances. Consequently, there is a requirement for more effective and accessible ways of improving knowledge and competence in health professionals (Liu et al., 2016). To date, IBL approaches have shown positive effects on health education outcomes through overcoming the above barriers (Cook et al., 2008).

Serious games have been defined as “interactive computer applications, with or without significant hardware components” that are designed to entertain while achieving changes in knowledge or skills. Methods to improve their entertainment value include dramatic tension, humour and challenge (Thompson, 2012). User engagement can also be improved through the inclusion of a narrative (Lu et al., 2016). Humour as an aid to nursing and medical education has been described in the literature (Baid and Lambert, 2010; Ziegler, 1999), while the use of games as a medium for humour may increase learners’ interest and motivation to learn (Baid and Lambert, 2010). As distinct from e-learning with limited user interaction (Graafland et al., 2014a), serious games can provide greater engagement with the educational content.

Use of serious game methodologies to deliver health professional education has been reported in previous studies (Graafland et al., 2014b; Wang et al., 2016; Castro-Sanchez et al., 2014). Educational and design frameworks are recommended for the development of games for health professional education (Akl et al., 2013; Graafland et al., 2014a). Strategies include application of knowledge in a safe environment that resembles real life (Akl et al., 2013), a degree of interactivity (Cain and Piascik, 2015), and entertainment (Thompson, 2012). These topics were considered in development and assessment of the e-learning tool in this study.

Most e-learning tools in health care have targeted specific groups, such as medical or nursing students, physicians or nurses (Boeker et al., 2013; Johnsen et al., 2016; Williams, 2014; Youngblood et al., 2008). We developed the VI to target nurses, doctors and pharmacists, the three main groups involved in use of medicines in hospitals. The specific educational content of the VI was clinical use of the glycopeptide antibiotic, vancomycin, given intravenously in hospitals for treatment of infections caused by MRSA. MRSA infections have high mortality and are resistant to conventional treatment with safer antibiotics such as penicillins, which usually do not require such specific administration and monitoring. Vancomycin is a commonly used antibiotic for treatment of MRSA infections (Rybak et al., 2009), but there are problems associated with its use. Those include the requirement for a loading dose (initial higher single dose) in serious infections, side effects when administered too rapidly, and the need to monitor vancomycin plasma levels (Antibiotic Expert Groups, 2014). As part of our ASP (Duguid and Cruickshank, 2010), local quality improvement activities identified gaps in competence around clinical use of vancomycin. Three main topics were identified from

those local activities and from previous studies: (1) dosing, including loading and maintenance (Swartling et al., 2012; Lomaestro, 2011; Phillips et al., 2016); (2) administration, such as compatible fluids and rate of infusion (Crowley et al., 2007; Phillips et al., 2016); and (3) TDM, including appropriate timing of blood sampling, target trough levels and required actions based on reported levels (Coleman and Wilson, 2015; Phillips et al., 2016; Cardile et al., 2015).

6.3.2 Aims of this study

The aims of this study were: (1) to report the design and implementation of a web-based, interactive e-learning tool providing education on the dosing, administration and TDM of vancomycin, (2) to assess health professionals' pre-intervention knowledge of vancomycin use in order to inform development of the e-learning tool, and (3) to assess health professionals' initial acceptance of the VI.

6.4 Methods

6.4.1 Setting

This prospective design and implementation study of a video-enhanced, web-based e-learning tool took place in ISLHD and South Eastern Sydney Local Health District (SESLHD), located in NSW, Australia. These health districts cover a geographic area of 6,331 square kilometres and have an estimated population of 1.17 million, reaching from central Sydney to three hours' drive south (New South Wales Health, 2010). The districts' 14 hospitals contain a total of 2500 beds and range from small rural facilities to

large tertiary metropolitan hospitals. A timeline of design, implementation and evaluation is shown in Figure 6.1.

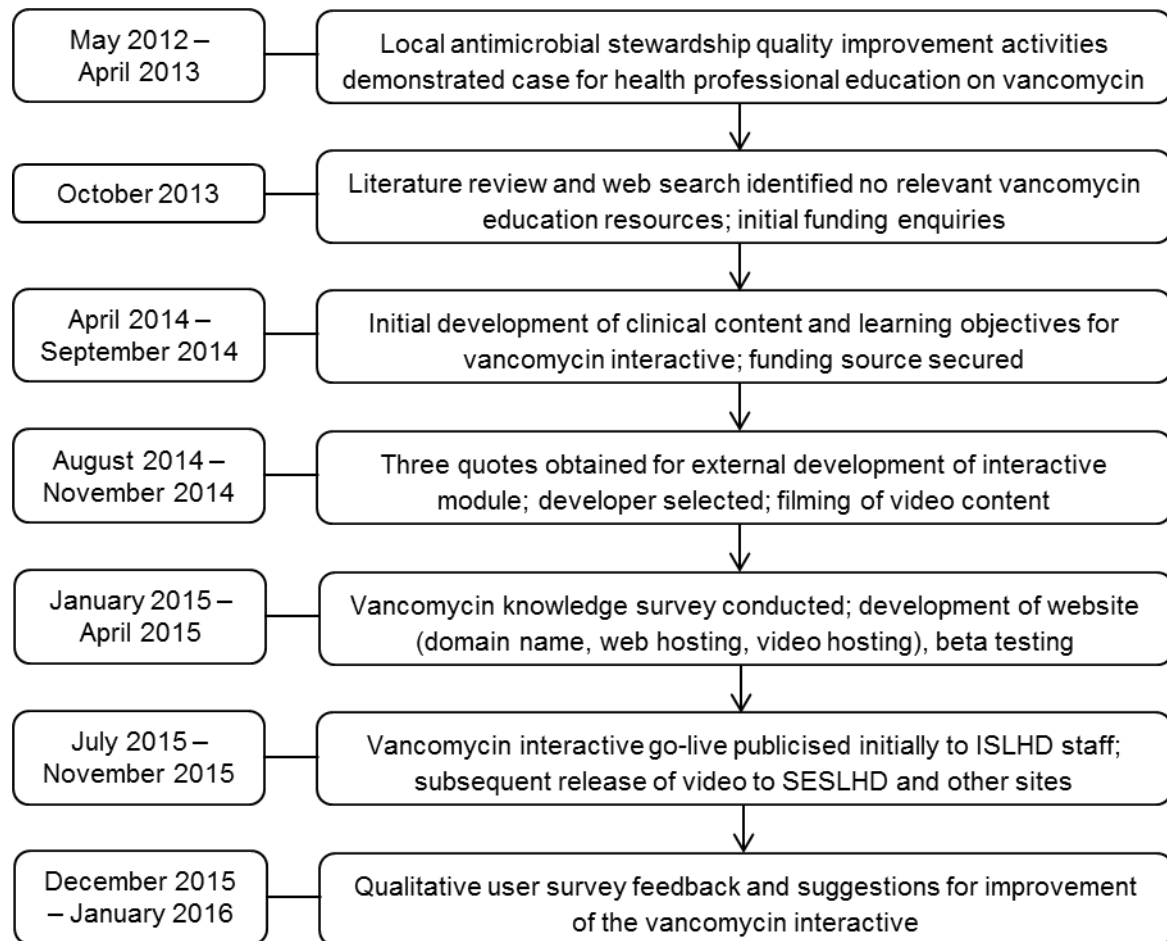


Figure 6.1: Timeline of VI design, implementation and evaluation

6.4.2 Web-based vancomycin knowledge survey

An anonymous open web-based survey was created using Survey Monkey® (Palo Alto, California, USA) to determine confidence, experience and knowledge of vancomycin, prior to the VI. The survey was developed locally by the AMS and educator pharmacists as part of routine activities, with input from the ID team. Clinical content was based on

the Australian *Therapeutic Guidelines: Antibiotic*, Version 15, 2014 (Antibiotic Expert Groups, 2014) and the *Australian Injectable Drugs Handbook*, Version 6, 2015 (Society of Hospital Pharmacists of Australia Publications Reference Group, 2015). Use of these references was required as part of the Australian hospital accreditation standards (Australian Commission on Safety and Quality in Health Care, 2011). Survey participants were nurses, doctors and pharmacists from the two health districts. A four-point Likert scale was used to determine levels of experience, confidence and knowledge on dosing, administration and TDM of vancomycin (Table 6.1). The survey was advertised using email and the districts' fortnightly newsletters. The survey link was open from 1 February 2015 to 30 June 2015 and participation was voluntary. Only one attempt was allowed on each question and users were directed to further reading material at completion of the survey. Nurses were expected to correctly answer questions on fluid compatibility and administration rate, since they were mainly responsible for administration of medicines in hospitals. Doctors were anticipated to correctly answer questions relating to dosing and TDM, arising from their role as prescribers. Pharmacists were expected to have a working knowledge of all aspects of clinical vancomycin use. The response rate to the survey was calculated from the number of respondents and the number of recipients on staff email groups.

Table 6.1: Vancomycin knowledge survey questions

1.	What is your profession?
2.	How much experience do you have with calculating doses of vancomycin?
3.	What do you think is the correct loading dose for vancomycin?
4.	What is an appropriate maintenance dose for vancomycin for a patient with a creatinine clearance of greater than 90mL/min?
5.	How confident are you to determine the administration rate for vancomycin?
6.	At what rate should vancomycin be administered to avoid red man syndrome?
7.	How confident are you to provide advice on vancomycin monitoring?
8.	When should the first level be taken for a dose of 1g 12hrly?
9.	What is the usual target range for vancomycin plasma trough levels?
10.	Did you refer to any resources to answer these questions?

6.4.3 Design and implementation of the VI

Similar to the survey, clinical content of the VI was developed locally, based on the *Therapeutic Guidelines: Antibiotic* (Antibiotic Expert Groups, 2014) and the *Australian Injectable Drugs Handbook* (Society of Hospital Pharmacists of Australia Publications Reference Group, 2015). The vancomycin knowledge survey informed in part the VI's educational content in the post-production phase, allowing finalisation of the multiple choice questions. An entertaining web-based educational tool was selected in the early development stage (mid-2013; Figure 6.1) for two reasons. The first was that there was already a health district requirement for staff to complete between 10 and 20 hours' mandatory training per year on other topics, and study investigators did not wish to

contribute to the burden of further web-based mandatory training. Rather, a brief, targeted, and light-hearted educational tool was thought to be more acceptable and beneficial for staff. Secondly, large distances between hospital sites meant that face-to-face education of health professionals was very resource intensive. The learning objectives of the VI for target users (nurses, doctors and pharmacists) were to improve knowledge of vancomycin dosing, administration and TDM. The VI did not address clinical indications for vancomycin, dosing in specialist areas such as intensive care and renal dialysis, use of continuous infusions or surgical prophylaxis.

A single interactive video was produced due to financial constraints; there was the expectation that all professional groups should have rudimentary knowledge of clinical vancomycin use. The VI (Copyright ISLHD) was hosted on the open website www.vancomycin.com.au (Bond and Crowther, 2015). Using the serious game design concepts of interactivity and entertainment, we presented a case study resembling real life interaction between a patient and a health professional. Dramatic tension between the two characters created the basis for the plot, along with the unprofessional behaviour of the modelled health professional. The interaction was also designed to be humorous, particularly through the special effect of “shrinking” the health professional, and references to William Shakespeare’s plays (Figure 6.2 and Figure 6.3). The concept was intended to appeal to health professionals who may feel they are at the mercy of their patients, a theme that emerged during the script-writing process.



Figure 6.2: Filming of the VI

The user interface consisted of video clips interspersed with interactive question and answer scenarios placed at the specific points, so that technical content felt organic to the narrative (Figure 6.4; Table 6.2). A correct answer allowed progression to the next section, whereas an incorrect answer resulted in a shaking screen and a sound effect. Data captured from answers to the interactive questions allowed for subsequent analysis. Only data from the targeted health professionals were included in the analysis; students and other participants were excluded. Additional questions in the VI, as distinct from the survey, related to compatibility of vancomycin with various fluids and clinical actions in response to different trough levels. Completion of the VI took approximately 10 minutes based on user testing.

Table 6.2: Vancomycin Interactive questions

1. What is an appropriate loading dose for Mrs Jones?
2. What is an appropriate regular dose for Mrs Jones?
3. What fluids should vancomycin be administered in? (more than one correct answer)
4. At what rate do you need to administer the vancomycin?
5. When should the first vancomycin level be taken for a patient receiving 1g 12hrly?
6. What is the target trough level?
7. If the level comes back as 35mg/L what may this mean? More than one answer may apply.
8. The first level comes back as 20mg/L. What should the next dose for this patient be and what is the dose interval?
9. If the level comes back as 26mg/L, what should the next dose and dose interval be for this patient?
10. The course length is likely to be 7 days based on the clinical response of the patient. When should the next level be taken? More than one answer may apply.



Figure 6.3: Dramatic tension created the basis for the VI's plot

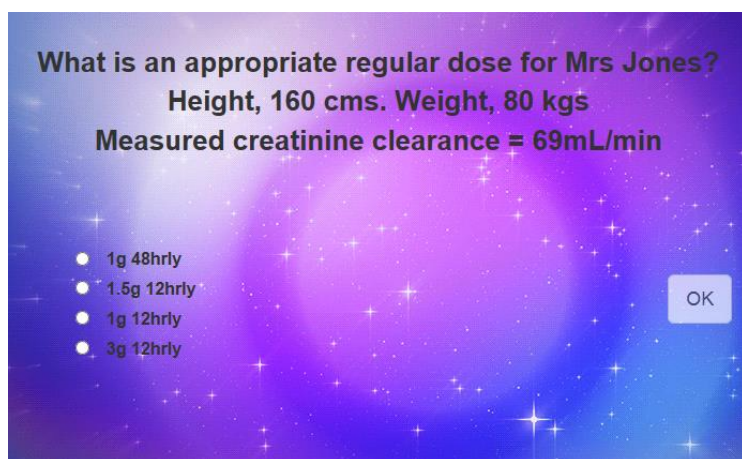


Figure 6.4: Example of user interface for an interactive question from the VI

Quotes for production were obtained from three developers in accordance with NSW Health policy, with financial support provided internally by the Clinical Governance Unit of the health district. Content development began in April 2014, and the video was filmed using professional actors in November 2014. Post-production modifications were made to the video up until release in July 2015. In early 2015 the website was established to promote improved access to the VI, and to include additional clinical content not contained in the VI. Testing of content and usability was performed by pharmacists and

ID doctors (n=8) at the study site, with feedback provided by email to the study investigators. Feedback from testers predominantly related to accuracy of the clinical content in the context of the narrative, and informed the final iteration of the VI. The first phase of dissemination and advertisement (email, newsletters, link on intranet homepage) to ISLHD staff occurred on 27 July 2015 (Figure 6.1) with the initial target audience estimated from organisational records to be 1000 staff. General release of the VI outside of ISLHD occurred on 17 November 2015. The final production cost was AUD\$15,000; time devoted to content development, testing, advertising, implementation, and evaluation was not included in those costs as it fell within usual activities for the pharmacy and infectious diseases department staff members involved in development of the VI.

6.4.4 User acceptance evaluation

Following release of the VI, qualitative survey responses were assessed to inform the investigators about user acceptability and suggestions for improvement. The qualitative survey was open between 1 December 2015 and 31 January 2016, in order to conclude prior to the annual intake of new junior doctors in February 2016 (Figure 6.1).

6.4.5 Outcome measures

The primary outcome measure was comparative vancomycin knowledge between health professions and self-reported levels of confidence and experience. Vancomycin knowledge responses from website data (not linked at a participant level) were also assessed and compared with the knowledge survey. In addition, qualitative feedback on the VI was evaluated using a five-point Likert scale and free text responses that were

grouped into key themes. Assessments were derived from survey responses and VI website data. Technical issues around compatibility with desktop and mobile operating systems and web browsers were also assessed. Reporting of outcomes on quantitative post-intervention survey data, clinical measures of quality vancomycin use such as therapeutic vancomycin plasma levels, and clinical outcomes related to vancomycin treatment was beyond the scope of this study.

6.4.6 Statistical analyses

Chi-square and Fisher's exact tests were used for proportions. Chi-square for trend was used to determine trend between professions for knowledge questions. Kruskal-Wallis and Mann-Whitney U-tests were used to examine total survey scores. For continuous data, normality was assessed using the Shapiro Wilk Statistic. A skewed distribution was denoted by $p < 0.05$. Kruskal Wallis and follow up Wilcoxon rank-sum tests were used to investigate between subjects effects with non-normal distributions. A multivariate analysis was performed to examine influential factors on correct survey responses. For each item a logistic regression was conducted followed by a multiple regression on the total score. For profession, nurses were allocated to the reference group, and self-reported "no experience/confidence" was used at the reference for the experience analysis. Statistical significance was accepted as $p < 0.05$. Additionally, a mediation analysis (Preacher and Hayes, 2008) was carried out to explore the mediating effects of vancomycin experience on the association between profession and knowledge (reflected by the total number of correct responses). For the mediation analysis, significance was determined by the 95% confidence of the regression coefficient, b . If the 95% CI did not contain 0 it was considered significant. The extent of mediation was reported as a

percentage, where a higher percentage reflects greater mediation. Statistical analyses were performed using Stata statistical software: Release 14 (Statacorp LP, College Station, TX, USA).

6.4.7 Ethics

Ethics approval was granted by the Joint UOW ISLHD Health and Medical Human Research Ethics Committee (EC00150; approval number HE15/005; Appendix F). The VI website contained a disclaimer that anonymous data collected from the video could be used for research purposes.

6.5 Results

6.5.1 Vancomycin knowledge survey prior to release of the VI

The response rate to the survey was 27% (577 responses from 2,147 email recipients). The response rates by profession were 24% (236/967) for nurses, 25% (271/1,070) for doctors and 64% (70/110) for pharmacists ($p < 0.001$).

As shown in Table 6.3, the median knowledge survey score for nurses was 2 (IQR 1-3), compared with 3 (IQR 3-4) for doctors and 4 (IQR 3-4) for pharmacists ($p < 0.001$). Pharmacists had greater total scores than both doctors ($p < 0.001$) and nurses ($p < 0.001$), while doctors had greater total scores than nurses ($p < 0.001$). For nurses, the most correctly answered questions were on administration rate (64% correct) and target trough range (58% correct), while only 19% of nurses answered the loading dose question

correctly. The most correctly answered question by doctors was on target trough range (86% correct). Pharmacists answered all responses correctly greater than 80% of the time.

Table 6.3: Number of correct responses to web-based vancomycin knowledge survey, n (%)

Survey question	Nurse n=236	Doctor n=271	Pharmacist n=70	p value	Total n=577
Loading dose	46 (19)	112 (41)	59 (84)	<0.001	217 (38)
Maintenance dose	58 (25)	126 (46)	58 (83)	<0.001	242 (42)
Administration rate	152 (64)	160 (59)	62 (89)	<0.001	374 (65)
First level timing	70 (30)	155 (57)	59 (84)	<0.001	284 (49)
Target trough range	136 (58)	234 (86)	65 (93)	<0.001	435 (75)
Median total score (IQR)	2 (1-3)	3 (3-4)	4 (3-4)	<0.001	3 (2-4)

Abbreviation: IQR, interquartile range

Multivariate analysis (Table 6.4) showed that for the loading dose question, pharmacists and doctors were more likely to achieve a correct response than nurses. A smaller variation between professions was seen for the administration rate question, with the comparison between pharmacists and nurses reaching significance. In addition, self-reported “very” and “reasonably” experienced health professionals were more likely to achieve a correct response. Similar associations between professions and experience levels were seen for maintenance dose, first level timing and trough level range (Table 6.4). Pharmacists self-reported more experience and confidence than doctors or nurses, which influenced the likelihood of a correct response.

Table 6.4: Multivariate analysis of vancomycin knowledge survey responses (n=577)

Topic		Profession			Experience/confidence			
		Nurse	Doctor	Pharm	1	2	3	4
		ref			ref			
Loading dose	OR	-	2.6	16.8	-	1.4	4.6	11.1
	(95% CI)		(1.7-4.1)	(7.9-35.7)		(0.8-2.7)	(2.4-8.6)	(3.3-36.9)
	p value	-	<0.001	<0.001	-	0.25	<0.001	<0.001
Maint dose	OR	-	2.5	12.1	-	1.0	2.2	3.3
	(95% CI)		(1.7-3.8)	(5.9-24.7)		(0.6-1.8)	(1.2-3.8)	(1.1-9.6)
	p value	-	<0.001	<0.001	-	0.85	0.01	0.03
Admin rate	OR	-	1.0	2.9	-	2.1	4.7	5.7
	(95% CI)		(0.6-1.4)	(1.3-6.4)		(1.4-3.3)	(2.9-7.6)	(0.2-1.1)
	p value	-	0.82	0.01	-	0.001	<0.001	<0.001
Level timing	OR	-	2.7	8.5	-	3.6	6.8	4.0
	(95% CI)		(1.9-4.1)	(4.0-17.7)		(2.1-5.9)	(4.0-11.6)	(1.4-10.9)
	p value	-	<0.001	<0.001	-	<0.001	<0.001	0.01
Trough range	OR	-	3.9	5.6	-	3.4	5.7	5.7
	(95% CI)		(2.5-6.1)	(2.1-15.1)		(2.1-5.6)	(3.2-10.0)	(1.2-26.5)
	p value	-	<0.001	0.001	-	<0.001	<0.001	0.03
Total correct	<i>b</i>	-	0.8	1.7	-		0.9 ^a	
	(95% CI)		(0.6-1.1)	(1.4-2.1)			(1.4-2.1)	
	p value	-	<0.001	<0.001	-		<0.001	

Abbreviations: ref, reference group for multivariate analysis; maint dose, maintenance dose; admin rate; administration rate; level timing, timing of first level; trough range, target range for plasma trough level, total correct; Pharm, Pharmacist (all levels); OR, odds ratio; CI, confidence interval; Experience/confidence: 1, none; 2, a little; 3, moderate; 4, very experienced/confident. *b*, regression coefficient; ^aaverage of responses to three vancomycin experience/confidence questions, therefore a multiple regression was performed for Total correct.

Subsequent mediation analysis revealed that vancomycin experience significantly mediated the effect of profession on total score (total indirect effect: $b = 0.63$, bias-corrected 95% CI 0.44 – 0.85). Approximately 58% of the profession effect was mediated by experience, where a higher percentage value indicates greater mediation.

6.5.2 Vancomycin Interactive

Responses to the VI were analysed using background website data received from 27 July to 14 November 2015, with ISLHD as the target population group. The initial dropdown question asking the user's profession was answered by 389 participants; 163 health professionals (42% of those answering the initial profession question) completed all ten questions (Table 6.5). The rate of correctly answered questions on first attempt was 65% for nurses, 68% for doctors and 82% for pharmacists, significantly higher in the pharmacist group ($p < 0.001$). Notably low numbers of correct responses were identified for the following three questions, averaged over the three professional groups: loading dose (39% correct), timing of first level (50%), and timing of subsequent levels (48%).

Table 6.5: Number (%) of correct answers on first attempt by nurses, doctors and pharmacists from VI data

Question	Nurse n=63	Doctor n=86	Pharmacist n=14	p value	Total n=163
1 – Loading dose	19 (30)	36 (42)	9 (64)	0.047	64 (39)
2 – Maintenance dose	50 (79)	59 (69)	11 (79)	0.32	120 (74)
3 – Compatible fluids	53 (84)	67 (78)	11 (79)	0.76	131 (80)
4 – Administration rate	56 (89)	55 (64)	14 (100)	<0.001	125 (77)
5 – Timing of first level	20 (32)	49 (57)	12 (86)	<0.001	81 (50)
6 – Target trough level	47 (75)	72 (84)	12 (86)	0.34	131 (80)
7 – Level of 35mg/L	43 (68)	68 (79)	14 (100)	0.02	125 (77)
8 – Level of 20mg/L	49 (78)	81 (94)	13 (93)	0.01	143 (88)
9 – Level of 26mg/L	46 (73)	55 (64)	12 (86)	0.20	113 (69)
10 – Subsequent levels	27 (43)	45 (52)	7 (50)	0.52	79 (48)
Average score	65%	68%	82%	<0.001	68%

p-values obtained using Chi-square for trend.

6.5.3 Comparison of responses between VI and web-based survey

The rates of correct response from the VI were significantly higher than the knowledge survey for maintenance dose (74% VI vs. 42% survey; $p<0.001$) and administration rate questions (77% VI vs. 65% survey; $p=0.004$). There was a slightly higher correct response rate for the question on target trough level (80% VI vs. 75% survey; $p=0.186$).

Uniformly low correct response rates were observed for the questions on loading dose (39% for VI vs. 38% for survey; $p=0.701$) and the timing of first level (50% VI vs. 49% survey; $p=0.89$). The question on timing of levels subsequent to the first level in the VI was answered correctly in 48% of cases; there was no equivalent question in the survey.

6.5.4 User acceptance evaluation of the VI

Among the 163 VI participants, 51 (31%) responses were received. Responses were predominantly positive, as shown in Table 6.6.

Table 6.6: Qualitative responses (%) following participation in the VI

Survey statement/question	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Using the VI has enhanced my knowledge (n=51)	11 (22)	29 (57)	8 (16)	3 (6)	0 (0)
Using the VI has improved my performance (n=50)	8 (16)	28 (56)	12 (24)	2 (4)	0 (0)

When users were asked, “What’s good about the VI in comparison to other e-learning modules?” 28 free text responses were received. Four responses (14%) related to not being able to load the video. Key themes from the remaining 24 responses (86%) were “entertaining”, “engaging”, “a lighter approach to learning”, “more real life”, and “held attention”. To the question, “Does the training provided by the VI meet your needs? If not, what can be improved?”, 23 free text responses were received. Sixteen respondents (70%) reported, “yes it met needs”; two (10%) stated issues loading VI; three users (13%) requested printable resources; one user was “not sure”; and one user requested more

information to be available when answering questions. All qualitative survey responses are provided in Table 6.7.

Table 6.7: Qualitative survey feedback on the Vancomycin Interactive

What was good about the Vancomycin Interactive in comparison to other e-learning modules? (28 responses)
<ul style="list-style-type: none"> • could not view • engaging • entertaining • Entertaining • entertaining easy to understand • fun and immediate answers available • Funny, not too much information • held attention. not just boring power point slides • i learnt stuff • Informative and entertaining • Interesting and memorable (due to jokes and cased based learning) • It concentrated on vancomycin • It was an entertaining lesson • it was engaging & entertaining :-) • It was fun and had a lighter approach to learning which was very nice! It was still very informative and educational, but the fun nature of Shirley made it more enjoyable to complete. • It was short and specific for vancomycin • it was very knowledgable session. it improves my confidence. the main thing is we are familiar with this medication and we quiet often uses at ward. • It wouldnt work on my work computer • more real life • no idea it wouldn't load • Provides a real world context • Step by step followed by questions • Unable to do vancomycin interactive. • Very entertaining • Video • Was interesting and interactive • Was short and funny • Was very interesting.....Fun way of learning with the jingle

Table 6.7 (cont)

Did the training provided by the Vancomycin Interactive meet your needs? If not, what can be improved? (23 responses)
<ul style="list-style-type: none">• yes (n=16)• a few case studies with some monitoring of levels would be useful• could not view• Good to be able to print a chart with formulas and normal levels• I think so, not sure if available but would like a summary of key points that can be printed out at end• It would be better to have more information before questions e.g. for dosing etc. Or at least have some explanation as to why the questions were wrong.• no idea it wouldn't load• not sure

6.6 Discussion

6.6.1 Principal findings

We have reported on the design, implementation and user evaluation of a novel web-based e-learning tool for education of health professionals on clinical use of the antibiotic vancomycin. The VI was developed for non-commercial use and targeted three health professional groups across multiple hospital sites. Responses from the survey that preceded the VI demonstrated a global lack of knowledge on the safe and effective use of vancomycin among nurses and doctors, justifying an IBL approach that was suitable for disparate geographical locations. Pharmacists were shown to be more knowledgeable on clinical vancomycin dosing, administration and TDM.

As expected, self-reported levels of confidence and experience were correlated with increased likelihood of correct responses to the knowledge survey questions. Responses

from the web-based knowledge survey and VI data were only similar for three of the five common questions, loading dose, timing of first level and the target trough level (Table 6.1 and Table 6.2). This may suggest that respondents equally understood those three questions in the VI and the knowledge survey. Responses to two questions, maintenance dose and administration rate, were significantly better in the knowledge survey compared with the VI. This could be caused by the respondents' different understanding about the survey questions presented in the two media or difference in knowledge level between the participants in the two surveys. Following implementation, qualitative survey responses demonstrated that the VI was well received by users, and was considered to be an engaging and entertaining method of improving knowledge. A small number of responses highlighted technical issues relating to not being able to load the video content, which were generally resolved through software upgrades.

Numerous studies have reported the development and evaluation of serious games for training health professionals, but few have targeted multiple professions (Wang et al., 2016; Graafland et al., 2012; Bergeron, 2008; Taekman and Shelley, 2010). One study reported development of a serious game on appropriate antibiotic use, but this was not specific to any particular antibiotic (Castro-Sanchez et al., 2014). Vancomycin was chosen as the topic for our web-based tool due to its frequency of use, and complexities associated with treatment of serious MRSA infections, the requirement for loading doses, TDM and subsequent dose adjustment. The VI in this study adopted some principles of serious game design (Graafland et al., 2014a), including interactivity and entertainment, and combined those with humour (Ziegler, 1999) to engage multi-professional users. Knowledge responses from the VI are promising, and further research is needed to

determine the reasons for difference in responses to questions between the classical knowledge survey and knowledge responses from VI website data.

Feedback from the majority of the participants suggested that the VI enhanced their vancomycin knowledge (79%) and improved their performance (72%). This supports the VI as a resource to provide healthcare professionals with training on clinical use of vancomycin. Qualitative responses were generally positive, further supporting the use of the VI for health professional education. The main challenges for implementation of the VI related to developing clinical content for the video that would remain applicable to all three professional groups, without creating a tool that would take too long to complete. Advertising the tool using different media was also challenging, as the tool was made available across two health districts with multiple hospitals, and the target professional groups may have preferred to receive alerts regarding content in different ways.

The creation of a brief, web-based, entertaining educational tool was the purpose of the project, whereby no further mandatory training burden was placed on staff. As distinct from existing local mandatory learning modules, the VI was intended for use among clinical staff involved in vancomycin use. Employing serious game design concepts may provide greater educational benefit than traditional computer-based learning methods through the use of greater interactivity, entertainment and scoring; however, further published comparisons are required (Wang et al., 2016). Our results suggest that pharmacists have the greatest level of knowledge on clinical vancomycin use. Therefore, in order to deliver the best learning outcomes for health professionals in this area, it is

recommended to combine face-to-face teaching with VI learning, using pharmacists as educators in the future.

6.6.2 Limitations of this study

We studied the logistics and design of an web-based e-learning tool incorporating interactive video content for health professional education relating to clinical use of the antibiotic vancomycin. Post-intervention knowledge and clinical outcomes were not reported here; these form the basis of ongoing research that will be reported separately. The use of an open website allowed for potential diffusion worldwide, since users outside our organisations may have found the VI using an internet search engine. In August 2015 the website was also shared on a professional network with members outside the targeted health district. As a result, there was some unintended use of the video prior to its general release. However, the greatest number of web sessions was from ISLHD, and employees of the target ISLHD hospitals may not have been physically located in the region while completing the VI.

Question design within the VI was limited to multiple choice and multiple answer questions. Further variation in question types such as open questions, as previously reported (Johnsen et al., 2016), could be made in future versions to improve immersion and interactivity. The inclusion of a formal testing process immediately before and after the e-learning tool may also have added some informative value on its effect and could inform future improvements. In addition, further scoring methodology, such as time limitation, competition and increasing difficulty could improve the robustness of the design (Wang et al., 2016). The Hawthorne effect may have introduced bias into the

study, whereby participants' behaviour may have been altered through their awareness of being measured. This bias may have been limited by participation being anonymous, and the primary intended aim for users being to further their vancomycin knowledge, rather than participation in a research project. Detailed economic analysis of the study was limited by the project forming part of usual educational activities for study investigators. As such, the total project cost was likely greater than the reported production cost.

There was relatively low uptake of the VI among clinical staff during the study period despite broad advertisement; this limited statistical power of the study and highlighted the challenge of using a new e-learning tool for delivery of non-compulsory training material to health professionals. Reasons for this probably related to the following: (1) the VI was not mandatory learning, so health professionals who did not regularly use vancomycin may not have been motivated to participate; (2) competing education priorities in those health professionals not otherwise intrinsically motivated to participate; (3) lack of time out from clinical responsibilities; (4) the likelihood that multiple staff completed the VI together, meaning that the VI's reach might have been greater than the results demonstrated; (5) the tool was not targeted towards a specific profession; and (6) not being able to access the VI using hospital computers, which may have hampered widespread use by health professionals during office hours. However, there were only four reports of the VI not loading from 51 survey responses, suggesting that the majority of participants could access the VI. While the free access website allowed for participation during working hours, there may have been less motivation to perform work-related education in this setting. It was expected that the greatest amount of participation would occur during working hours on hospital computers. Clinical

indications for vancomycin were not addressed by the VI, as its primary purpose was to improve knowledge once the decision to prescribe had been made.

Our study presented a model for adopting serious game concepts in combination with humour to develop and conduct web-based health professional education in a light-hearted, interactive and entertaining way. This model may be useful in settings where use of face-to-face education is limited by resources and geography. As the VI learning material was made available around the world, it showcased another significant benefit of open e-learning resources. Health professionals and health care organisations with the same learning needs can reuse the material we have published rather than expending resources to develop similar material.

6.6.3 Conclusions

We demonstrated a novel web-based e-learning tool that used humour and some game design principles to deliver health professional education on the commonly used antibiotic vancomycin. The VI was well accepted by users, and was thus useful for delivering the intended health professional education. Future learning needs for different professional groups were identified through both the web-based knowledge survey and VI data. This will allow tailoring of face-to-face education programs, in addition to subsequent versions of the VI that will embed robust gaming methodology. Further research will be aimed at measuring the effect on knowledge of the VI compared with a traditional email intervention, and examining the impact of the VI on clinical vancomycin use.

6.6.4 Acknowledgements

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Conflicts of interest

The authors declare no conflicts of interest.

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7 Evaluating the effect of a web-based e-learning tool for health professional education on clinical vancomycin use: a comparative study

Article under review in *Journal of Medical Internet Research: Medical Education* (March 2017).

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7.1 Summary statement

This chapter further investigates the use of technology for providing education to health professionals in relation to antimicrobial use, a theme that builds on those described in Chapters 5 and 6. The VI is compared with a standard educational email intervention in terms of clinical vancomycin knowledge use. The outcome measure of vancomycin plasma levels is also evaluated in relation to the VI. Clinical outcomes of antimicrobial use as balancing measures have also been explored in Chapters 2, 3, 4, and 5.

7.2 Abstract

7.2.1 Background

IBL for health professional education is increasing. It offers advantages over traditional learning approaches, as it enables learning to be completed at a time convenient to the user and improves access where facilities are geographically disparate. We developed and implemented the VI e-learning tool to improve knowledge on the clinical use of the antibiotic vancomycin, which is commonly used for treatment of infections caused by MRSA.

7.2.2 Objectives

The aims of this study were to evaluate the effect of the VI e-learning tool on: (1) survey knowledge scores and (2) clinical use of vancomycin among health professionals.

7.2.3 Methods

We conducted a comparative pre-post intervention study across the 14 hospitals of two health districts in New South Wales, Australia. A knowledge survey was completed by nurses, doctors and pharmacists before and after release of a web-based e-learning tool. Survey scores were compared with those obtained following a traditional educational intervention in the form of an email update. Survey questions related to dosing, administration and monitoring of vancomycin. Outcome measures were survey knowledge scores among the three health professional groups, vancomycin plasma trough levels and vancomycin approvals recorded on a CDSS.

7.2.4 Results

Survey response rates were 27% (577/2147) pre-intervention and 8% (177/2147) post-intervention. The VI was associated with an increase in knowledge scores among nurses (mean 1.67 out of 5 to 2.35/5; $p<0.001$) but not among other professional groups. The comparator email update was associated with an increase in knowledge scores among the overall respondent group (mean 2.85/5 to 3.3/5; $p=0.02$) and among doctors (mean 2.83/5 to 3.29/5; $p=0.04$). Participants who referred to web-based resources while completing the e-learning tool achieved higher overall scores than those who did not ($p<0.001$). The e-learning tool was not shown to be significantly more effective than the comparator email in the clinical use of vancomycin, as measured by plasma levels within the therapeutic range.

7.2.5 Conclusions

The e-learning tool was associated with improved knowledge scores among nurses, whereas the comparator email was associated with improved scores among doctors. This implies that different strategies may be required for optimising the effectiveness of education among different health professional groups. Improvements to design and evaluation methodology are proposed to increase the likelihood of a demonstrable effect from e-learning tools in the future.

7.2.6 Keywords

Nursing education; pharmacy education; medical education; continuing education; survey methods; anti-bacterial agents.

7.3 Introduction

7.3.1 Internet-based learning

Traditional face to face approaches to health professional education are being challenged by busy trainee schedules, involving increased clinical demands and decreased available time (Cook et al., 2010; Wang et al., 2016). These barriers can be addressed through the use of internet-based learning (IBL) approaches, which can be completed at a time convenient to the user (Cook et al., 2008). IBL may also be useful where health professional education is required across geographically disparate hospital locations. Effective IBL tools should provide entertainment and supply the user with knowledge, skills or attitudes useful in real life (Bergeron, 2006). Recently there has been considerable development in novel IBL methodologies for health professional education (such as serious games) with common topics relating to surgical skills training, critical care and emergency triage (Graafland et al., 2012; Wang et al., 2016). Some studies showed improvements in test scores (Wang et al., 2016); however, study design was heterogeneous, and none focused on the antibiotic vancomycin as an educational target.

7.3.2 Vancomycin education

Vancomycin is the main antibiotic used for treatment of infections caused by MRSA (Antibiotic Expert Groups, 2014). Problems associated with vancomycin use across multiple professions include the requirement for a loading dose in serious infections, side effects when administered too rapidly, and the need to monitor vancomycin plasma levels (or concentrations) (Antibiotic Expert Groups, 2014). Therefore, several studies have

described interventions to improve clinical use of vancomycin (Phillips et al., 2016; Melanson et al., 2013; Swartling et al., 2012; Coleman and Wilson, 2015; Hamad et al., 2015; Crowley et al., 2007; Dib et al., 2009; Li et al., 2012). Specific topics addressed in those studies were dosing (Phillips et al., 2016; Swartling et al., 2012; Hamad et al., 2015; Li et al., 2012), administration (Phillips et al., 2016) and therapeutic drug monitoring (TDM) (Phillips et al., 2016; Melanson et al., 2013; Swartling et al., 2012; Coleman and Wilson, 2015; Crowley et al., 2007; Dib et al., 2009). Educational targets were nurses, doctors, or pharmacists, with one TDM study conducting multidisciplinary interventions (Crowley et al., 2007). In a previous study we described the design and implementation process of a web-based e-learning tool (Vancomycin Interactive; VI©) that employed serious game design concepts including interactivity and entertainment to provide education on vancomycin (Bond et al., 2017). To our knowledge, the current study is the first to compare outcomes of a vancomycin e-learning tool with a standard didactic email intervention.

7.3.3 Aims of this study

The aims of this study were to assess the VI e-learning tool versus standard email update for: (1) effects on health professionals' vancomycin knowledge; and (2) effects on quality of vancomycin use measured by both vancomycin plasma trough levels and approvals for use recorded on a computerised clinical decision support system (CDSS) (Guidance Group, 2013).

7.4 Methods

This comparative pre-post intervention study took place in ISLHD (intervention site; 1000 total beds; 700 acute beds) and SESLHD (comparator site; 1500 total beds; 1200 acute beds), located in New South Wales (NSW), Australia (Figure 7.1). These health districts cover a geographic area of 6,331 km² and have an estimated population of 1.17 million, reaching from central Sydney to 3 h drive south (New South Wales Health, 2010). The districts' 14 hospitals range from small rural facilities to large tertiary metropolitan hospitals. The comparator site was selected due the following: a shared information technology platform with the intervention site; geographical proximity, and existing clinical and professional networks.

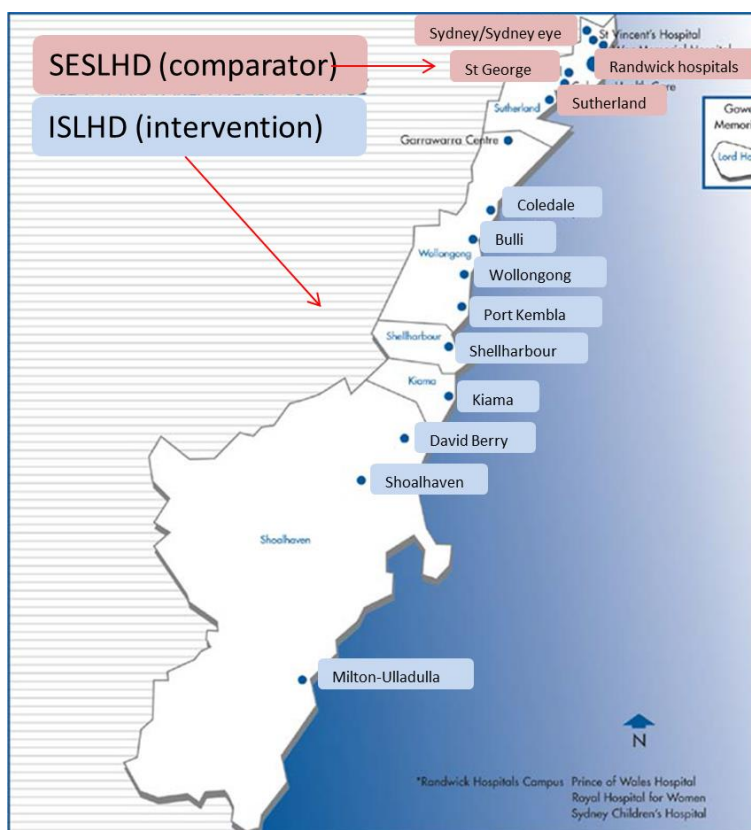


Figure 7.1: Map of intervention and comparator sites

7.4.1 Pre-and post-intervention vancomycin knowledge survey

An anonymous web-based survey was created using Survey Monkey® (SurveyMonkey Inc, Palo Alto, CA) to determine pre-intervention experience/confidence and knowledge of vancomycin use among nurses, doctors and pharmacists across two health districts (Bond et al., 2017). A four-point Likert scale was used to determine levels of experience and confidence relating to knowledge questions on dosing, administration and monitoring of vancomycin (Table 6.1). Post-intervention, a second survey with the same questions was sent to the intervention and comparator sites. User testing indicated that pre-intervention survey would take around two minutes to complete and the post-intervention surveys would take three minutes, since additional user feedback was sought on the VI and comparator email. Requests for survey participation are included as Figure 7.2 and Figure 7.3. A survey question on resources used to answer the survey was also analysed.

“Dear health professional (nurse, doctor, pharmacist),
Please take two minutes to complete a brief knowledge survey on the dosing, administration and monitoring of vancomycin.
This survey will help us to develop a vancomycin learning module targeted to your needs at SESLHD and ISLHD Hospitals.
<https://www.surveymonkey.com/s/vancomycin>
We would be grateful for your time to answer 10 quick questions.
Thank you”

Figure 7.2: Pre-intervention survey request emailed to staff at intervention/ comparator sites

Dear colleague,

Please take 3 minutes to complete this second survey on the anti-MRSA antibiotic vancomycin. We would love to know if the VI/vancomycin email update was useful, and how we can improve antibiotic education in the future. Answers will remain confidential.

To complete the survey please click: <https://www.surveymonkey.com/r/vancomycin>

Thanks!”

Figure 7.3: Post-intervention survey request emailed to staff at intervention/ comparator sites

7.4.2 VI and clinical email update

Educational content was developed locally for the VI on dosing, administration and TDM of vancomycin (Antibiotic Expert Groups, 2014; Society of Hospital Pharmacists of Australia Publications Reference Group, 2015). The learning objectives of the VI for target users (nurses, doctors and pharmacists) were to improve knowledge of vancomycin dosing, administration and TDM. The VI (ISLHD) (Bond and Crowther, 2015) depicted a case study involving interaction between a patient and a health professional, both played by professional actors. The user interface consisted of video clips interspersed with interactive question and answer scenarios (Table 6.2). User testing indicated that the VI would take approximately 10 minutes to complete. An email (taking 2-3 minutes to read) with the same clinical content and learning objectives was developed as a comparator intervention (Figure 7.4). To allow for the differences in the two media, there were some minor variations in clinical content between the VI and email that related to administration of vancomycin.

Release and advertisement of the VI (email, newsletters, link on intranet homepage) to the intervention site occurred on 27 July 2015. The clinical email update was then sent to nurses, doctors and pharmacists at the comparator site (Figure 7.4). Following completion of the second survey, the VI website was also advertised to the comparator site.

“Dear health professional (nurse, doctor, pharmacist),

There have been some **important updates** to the adult guidelines for dosing, administration and monitoring of intravenous **vancomycin**, commonly used for the treatment and prevention of infections caused by MRSA.

Please see below for the key points:

DOSING

A **loading dose** is recommended, particularly in patients with serious infections who are critically ill. A dose of 25-30 mg/kg is appropriate in most situations.

For **maintenance doses** of vancomycin in an average weight patient (70kg):

Creatinine clearance (mL/min)	Starting maintenance dosage	Timing of trough plasma level
more than 90	1.5 g 12-hourly	before the fourth dose
60 to 90	1 g 12-hourly	before the fourth dose
20 to less than 60	1 g 24-hourly	before the third dose
less than 20	1 g 48-hourly	48 hours after the first dose

- For intermittent dosing of vancomycin, an appropriate maintenance dose is 15-20 mg/kg (actual bodyweight). Use the Cockcroft-Gault formula or online calculator to approximate creatinine clearance.

ADMINISTRATION

Vancomycin should be administered by slow infusion at a rate of **10 mg/min**.

MONITORING

- The recommended trough level for vancomycin is **15 to 20 mg/L** for most infections.
- Before interpreting the result, check that the timing of the trough sample was appropriate (i.e. before the last dose was given). In patients receiving vancomycin 12hrly, do not wait for the trough concentration result before giving the next scheduled dose.
- Adjustment of vancomycin dosage in adults:

Trough plasma level	Dosage adjustment
less than 10 mg/L	Increase dosage by adjusting either the dose or the dose interval.
10 to 14 mg/L	For patients with uncomplicated infection who are clinically improving, maintain current dosage. For patients with complicated infection, increase dosage by adjusting either the dose or the dose interval to achieve a trough concentration of 15 to 20 mg/L.
15 to 20 mg/L	Maintain current dosage.
21 to 25 mg/L	Maintain current dosage, or reduce dosage by adjusting either the dose or the dose interval, or withhold dose.
more than 25 mg/L	Withhold dose until trough concentration is less than 20 mg/L and seek expert advice.

For any questions please contact ...”

Clinical content based on *Therapeutic Guidelines: Antibiotic*, Version 15 (Antibiotic Expert Groups, 2014).

Figure 7.4: Clinical email update sent to staff at the comparator sites

7.4.3 Vancomycin trough plasma levels and approvals on the CDSS

Vancomycin plasma levels from a four month period before and a two month period after the VI and comparator email were analysed to determine changes in the proportion of levels in the therapeutic range. The post-intervention period was limited to two months in order to conclude prior to the annual intake of new junior doctors. Criteria for dose adjustment were as follows: (1) 0-9 mg/L, increase dose; (2) 10-14 mg/L, maintain or increase dose depending on severity of infection and clinical status; (3) Maintain current

dose (4) 20-25 mg/L, maintain or reduce dose depending on severity of infection and clinical status; (5) >25 mg/L, withhold dose until trough level less than 20 mg/L and seek expert advice (Antibiotic Expert Groups, 2014). The number of vancomycin levels as a proportion of the total number of vancomycin CDSS approvals was also analysed to determine frequency of vancomycin use. Pharmacy dispensing software did not allow for patient-level data on vancomycin dispensing to be analysed, as vancomycin was distributed as ward stock in some hospitals. Hence, vancomycin CDSS approvals were used as a surrogate indicator for total vancomycin use.

7.4.4 Outcome measures

We compared total vancomycin knowledge survey scores pre- and post-intervention, within and between intervention and comparator sites. The number of vancomycin levels in the therapeutic range, the median number of vancomycin levels and ratio of vancomycin levels to CDSS vancomycin approvals between sites were also analysed.

7.4.5 Statistical analyses

Chi-square and Fisher's exact tests were used for proportions. For continuous data, normality was assessed using a Skewness/Kurtosis statistic (D'Agostino et al., 1990). A skewed distribution was denoted by $p < 0.05$. Kruskal-Wallis and follow up Wilcoxon rank-sum tests were used to investigate between effects with non-normal distributions. Multivariate analysis was performed to examine influential factors (profession, site, pre- or post-intervention) on correct survey responses. Statistical analyses were performed using Stata statistical software: Release 14 (Statacorp LP, College Station, TX, USA).

7.4.6 Ethics

Ethics approval was granted by the Joint UOW and ISLHD Health and Medical Human Research Ethics Committee (EC00150), approval number HE15/005 (Appendix F). The VI website contained a disclaimer that anonymous data collected from the video could be used for research purposes.

7.5 Results

7.5.1 Vancomycin knowledge survey

The response rate to the pre-intervention survey was 27% (577 responses from 2147 email recipients). The response rates by profession were 24% (236/967) for nurses, 25% (271/1070) for doctors and 64% (70/110) for pharmacists ($p<0.001$); previously reported (Bond et al., 2017). Post-intervention, there were 177 survey responses (8% response rate), comprising 88 nurses, 69 doctors and 20 pharmacists ($p<0.001$).

Univariate analysis demonstrated that pre-intervention, there was a higher median survey score for the comparator site (median 3/5; IQR 2-4; mean 2.85) than for the intervention site (2/5; IQR 1-3; mean 2.51; $p=0.01$). Post-intervention survey scores were also higher for the comparator site (median 3/5; IQR 2-4; mean 3.3) than for the intervention site (median 3/5; IQR 2-4; mean 2.71; $p=0.06$).

The median knowledge survey score for nurses increased post-VI ($p<0.001$; Table 1). No significant differences pre- and post-VI were observed for doctors, pharmacists or for combined health professionals. At the comparator email site, the median knowledge survey score increased post-intervention for combined health professionals ($p=0.02$) and for doctors ($p=0.04$).

7.5.2 Resources used to answer survey questions

To the question, “Did you refer to any resources to answer these questions?,” 595/754 (79%) participants responded “no”. Out of those 595, 424 (71%) self-reported that they guessed some or all of the answers, whereas 171 (29%) reported that they knew the answers. The remaining 159/754 (21%) respondents self-reported that they referred to resources for answering the questions. The resources quoted were local guidelines (49/159 [31%]) and the Australian Medicines Handbook or Therapeutic Guidelines: Antibiotic (110/159 [69%]).

Table 7.1: Pre- and post-intervention median knowledge survey score, n (IQR)

Profession	VI intervention site			Comparator email site		
	Pre; n=278	Post; n=107	p value	Pre; n=299	Post; n=70	p value
Nurse	2/5 (1-2)	2/5 (1-3)	<0.001	2 (1-3)	3 (2-4)	0.17
	Mean: 1.67	Mean: 2.35		Mean: 2.30	Mean: 2.71	
Doctor	3 (2-4)	4 (2-4)	0.28	3 (2-4)	4 (2-4)	0.04
	Mean: 3	Mean: 3.29		Mean: 2.83	Mean: 3.29	
Pharmacist	5 (4-5)	4 (4-5)	0.40	5 (4-5)	5 (4-5)	0.87
	Mean: 4.24	Mean: 3.89		Mean: 4.39	Mean: 4.27	
Total	2/5 (1-4)	3/5 (2-4)	0.24	3 (2-4)	3 (2-4)	0.02
score	Mean: 2.51	Mean: 2.71		Mean: 2.85	Mean: 3.3	

7.5.3 Multivariate analysis of knowledge survey scores

Several factors were associated with an increased knowledge survey score. Compared with nurses, pharmacists (regression coefficient 1.93; 95% confidence interval 1.63-2.23; $p<0.001$) and doctors (coeff 0.89; 95% CI 0.70-1.09; $p<0.001$) had increased likelihood of a higher survey score. Post-intervention survey participation was also associated with a higher score (coeff 0.41; 95% CI 0.20-0.62; $p<0.001$) than pre-intervention. Referring to online resources was associated with a higher score compared with responses where participants self-reported that they knew or guessed the answers (coeff 0.98; 95% CI 0.75-1.20; $p<0.001$). The comparator site was not significantly associated with increased likelihood of higher survey scores (coeff 0.16; 95% CI -0.02-0.34; $p=0.08$).

7.5.4 Vancomycin TDM

From 1 January to 30 April 2015 there were 429 vancomycin trough plasma levels taken at the intervention site (ISLHD; 1000 beds) and 1571 levels for the comparator site (SESLHD; 1700 beds). During the post-intervention period 1 December 2015 to 31 January 2016, there were 151 levels reported at the intervention site and 316 levels at the comparator site. As shown in Table 7.2, there were no significant post-intervention differences in the proportion of vancomycin levels in the sub-therapeutic (0-9mg/L), therapeutic (10-14, 15-20, 21-25 mg/L) or supra-therapeutic (>25 mg/L) ranges. There were increases in the number of levels in the high-therapeutic range (20-25 mg/L) at both sites; however, those differences did not reach statistical significance. There were no significant pre-post intervention differences in median vancomycin levels at the intervention site or comparator site (Table 7.2).

Table 7.2: Pre- (4 months) and post-intervention (2 months) vancomycin plasma trough levels for intervention and comparator sites, n (%)

Trough level (mg/L)	VI intervention site			Comparator email site		
	Pre	Post	p	Pre	Post	p
	n=429	n=151	value	n=1571	n=316	value
0-9 (sub-therapeutic)	48 (11)	17 (11)	0.98	259 (16)	50 (16)	0.77
10-14 (low therapeutic)	91 (21)	28 (19)	0.49	362 (23)	62 (20)	0.18
15-20 (therapeutic)	168 (39)	54 (35)	0.46	515 (33)	98 (31)	0.54
21-25 (high therapeutic)	72 (17)	36 (24)	0.06	260 (17)	66 (21)	0.06
>25 (supra-therapeutic)	50 (12)	16 (11)	0.73	175 (11)	40 (13)	0.44
Median trough level (IQR)	18 (13-21)	17 (13-22)	0.62	16 (12-21)	17 (12-22)	0.14

VI, Vancomycin Interactive; IQR, interquartile range.

7.5.5 Vancomycin trough plasma levels compared with vancomycin CDSS approvals

The proportion of vancomycin trough levels to vancomycin CDSS approvals at the intervention site decreased from 429/399 pre-intervention (1.1 levels for every vancomycin approval) to 151/196 post-intervention (0.8 levels/approval). At the comparator site, the proportion of vancomycin levels to vancomycin CDSS approvals decreased from 1571/399 pre-intervention (3.9 levels/approval) to 314/199 post-intervention (1.6 levels/approval).

7.6 Discussion

7.6.1 Principal findings

This study compared the educational effect of an interactive web-based e-learning tool with a comparator email update. Altogether, the e-learning tool did not result in improved knowledge survey scores or clinical vancomycin use when compared to the email.

However, the e-learning tool was associated with improved survey scores among nurses, whereas the comparator email update was associated with improved scores among doctors. Multivariate analysis showed that survey scores did not differ between the intervention and comparator sites. Not unexpectedly, pharmacists and doctors had higher overall knowledge scores than nurses due to the greater number of questions considered relevant to those groups. Participants who referred to web-based resources while completing the survey had higher survey scores than those who did not.

Concerningly, only about one third of pre- and post-intervention vancomycin levels taken at both sites fell within the recommended therapeutic range of 15-20 mg/L. This figure rose to 73% when the ranges 10-14 mg/L, 15-20mg/L and 21-25 mg/L were combined, which includes all potential recommended therapeutic ranges (Antibiotic Expert Groups, 2014). The proportion of vancomycin levels to CDSS approvals decreased at both sites, perhaps signifying a reduction in the ordering of unnecessary levels, or shorter vancomycin courses requiring fewer levels. A greater proportion of levels/approvals was observed at the comparator site in both pre- and post-intervention phases, which may have resulted from differences in acuity between sites.

In previous studies, strategies for improving the clinical use of vancomycin have included use of loading doses (Li et al., 2012), implementation of guidelines (Swartling et al.,

2012), education (Phillips et al., 2016; Coleman and Wilson, 2015; Dib et al., 2009), and clinical decision support systems (Hamad et al., 2015; Crowley et al., 2007; Melanson et al., 2013). None of those educational interventions incorporated a web-based e-learning tool, and the predominant methodology was uncontrolled pre-post intervention at single hospital sites. One study has reported development of a serious game to improve general antimicrobial prescribing but it did not focus on vancomycin (Castro-Sanchez et al., 2014). A review of educational games for health professionals emphasised the need for more research with improved study methodology (Akl et al., 2013). Our study differed in its multisite approach, comparison of e-learning tool with a standard email intervention, and targeting of multiple health professional groups.

7.6.2 Interpretation of results

The difference in efficacy between the VI (improved nurses' scores) and the email (improved doctors' scores) may have arisen from nurses' increased familiarity and engagement with online learning modules, whereas for doctors a didactic learning style may be more suitable. Additionally, the short time to read a clinical update email may have been more convenient for doctors. Referring to resources was associated with improved survey scores, which emphasises the importance of guideline access in the clinical setting. Some aspects of our study design may be applicable to facilities where there are geographic barriers to use of face-to-face education, such as rural and regional hospitals. Some improvements to the structure of the VI through greater application of serious game methodology are proposed (Table 7.3), including more interactivity, scoring and competition (Graafland et al., 2014; Thompson, 2012). Those features could result in a greater level of user acceptance and effectiveness.

7.6.3 Study limitations

There were some underlying differences in baseline vancomycin knowledge between intervention and comparator sites as detected in the univariate analysis; however, those did not retain significance in the multivariate analysis. Also, the total number of vancomycin levels at the comparator site was considerably higher, which may be due to differences in case mix (number of acute beds), antimicrobial use and background educational culture. However, the proportion of satisfactory levels (i.e. those in therapeutic range) did not differ between the sites. Furthermore, similar sizeable reductions in the number of vancomycin levels ordered were experienced at both sites. Some of this reduction may have been associated with seasonal variation of vancomycin use, although unlike other antibiotics, vancomycin is not typically associated with strong seasonal variation (Australian Commission on Safety and Quality in Health Care, 2015). The low response rate to the post-intervention survey limited the power of pre-post intervention comparisons. Potential reasons for this reduction include the perception of staff that the post-intervention survey request concerned the pre-intervention survey, despite clarifications that were provided in the email title and text, and appropriate advertisement in staff newsletters. We note that the proportions of different health professionals were similar in the two time periods. In addition, the denominator included all targeted health professionals including those not involved in the day-to-day clinical use of vancomycin, which is likely to have reduced the response rate. The higher scores from the post-intervention survey may have resulted from participant bias; i.e. only more experienced and enthusiastic staff may have responded to the second survey. Time-dependent bias may also have influenced some of the improvement in

survey scores, whereby increased time in a clinical role may have resulted in greater knowledge of vancomycin use over the study period. A crossover design might have partially alleviated this factor, but was not possible in our case due to the rotation of junior doctors between the two sites.

There were some minor variations in clinical content between the VI and email; however, they related only to administration of vancomycin and references used for development of content were the same for both interventions. Participants who referred to guidelines while completing the survey attained higher scores than those who did not. Although this was unavoidable in a pragmatic study, it was still a desirable outcome as those participants were using recommended national or local guidelines. The time to complete the e-learning tool (10 minutes) was longer than the email update (2-3 minutes); the duration of the email may have been more appropriate in a busy clinical context. As reported in our previous study (Bond et al., 2017), there was low uptake of the VI during the study period, and we did not measure the number of comparator emails read by staff. There may have been some word of mouth leakage of the VI to the comparator site; however, study data collection was completed prior to the junior doctor rotation. Given the use of paper medications charts, the number of CDSS approvals was used as a surrogate for vancomycin prescribing. We did not examine quality measures of vancomycin use such as time to first therapeutic level, levels obtained at steady-state, or clinical outcomes associated with the intervention; further research aims to examine these effects. Linkage of survey-participant responses was desirable but was not achievable within the ethical requirement for an anonymous survey. Based on those limitations and the mixed results of our study, we propose a checklist that, subject to validation, may

improve the likelihood of demonstrating significant effects from an e-learning tool (Table 7.3).

Table 7.3: Proposed development and evaluation checklist for health professional e-learning tools

	Perform qualitative research prior to design to determine learning needs of the target group
	Target clinical content to a specific health professional group
	Apply a theoretical educational framework to include serious game design elements such as entertainment, interactivity, scoring, and competition
	Use identifiable surveys where possible to allow individual linkage of pre- and post-intervention survey results
	Allow for sufficient time post-intervention to collect data on knowledge and user acceptability
	Limit time required to complete the application (<5 minutes) in the context of a busy clinical environment and acknowledging competing education priorities
	Improve access to the e-learning tool through open access websites, development of the tool as an app and shortcuts through the local intranet
	Record pre- and post-intervention data that can suggest both effectiveness and non-effectiveness, including quantitative clinical outcomes
	Develop a comprehensive advertisement and dissemination plan, to include email, social media, newsletters, hospital grand rounds, quick links on hospital computers
	Optimise search engine capacity
	Select appropriate site for comparison with the e-learning tool
	Comprehensive beta-testing by target end users
	Collect relevant from the e-learning tool's data feed

7.6.4 Conclusions

Different health professional groups can be educated by using different targeted learning approaches. Significant challenges can be experienced during design and evaluation of comparative e-learning research. Further studies should aim to improve structural elements of e-learning tools and enhance evaluation through an approach governed by a newly proposed checklist.

7.6.5 Acknowledgements

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Conflicts of interest

The authors declare no conflicts of interest.

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8 General discussion

8.1 Preamble

The research in this thesis by journal article compilation has extended current knowledge of antimicrobial stewardship. The three primary aims were achieved during the course of this research project. Firstly, an educational approach to improving antimicrobial use was developed and evaluated at the individual, department, hospital and health district level. Prevention of infection, treatment of infection and a serious adverse effect of antimicrobial use were presented to demonstrate the value of this approach. Secondly, AMS education and evaluation strategies applicable to multisite and rural and regional settings were developed. Clinically meaningful outcome measures were targeted, such as duration of antimicrobial therapy, LOS and mortality. Thirdly, technology for improving ASPs was developed, implemented and evaluated, including: a CDSS to enhance education and reporting, use of email in research and development of a web-based e-learning tool for education of health professionals. The results suggest that: common educational methods can be used to improve hospital antimicrobial use across different clinical settings and organisational levels; patient-related outcomes should be measured in addition to processes when evaluating AMS interventions; and technological innovations can enhance the effectiveness of ASPs.

This concluding chapter provides an overview of project findings, followed by an outline of the implications, strengths and limitations of this work. Recommendations for future research are presented, followed by the thesis conclusions.

8.2 Overview of findings

Improving antimicrobial use in humans forms an important part of the Australian national strategy to address AMR (Australian Government, 2015). Hospital AMS initiatives should be targeted towards high-use areas, such as surgical prophylaxis and treatment of common infections such as CAP (Duguid and Cruickshank, 2010; Australian Commission on Safety and Quality in Health Care, 2015). In Chapter 2, an educational approach was employed to discontinue prophylactic gentamicin use for insertion and removal of urinary catheters in orthopaedic surgery patients. Use of gentamicin in this setting was considered inappropriate according to national guidelines (Antibiotic Expert Group, 2010), but was an embedded practice at the time of intervention. The requirement for peer education and review, and the potential for medico-legal considerations to influence behaviour change among senior doctors were outlined in this chapter.

CAP remains a leading cause of hospitalisation and death worldwide (Postma et al., 2015). Inappropriate use of antimicrobials for the treatment of CAP can result in emergence of resistant pathogens such as MRSA (Paterson, 2004). Chapter 3 reported an approach for improving antimicrobial treatment of CAP that included use of timely measurement and feedback to individual clinicians via email, education at departmental meetings, and auditing of compliance with guidelines. Based on those interventions, a reduction in median duration of CAP therapy was demonstrated, driven by shorter courses of oral antimicrobials. Excessive duration of therapy is one of the most common reasons for inappropriate antimicrobial use in Australia (Australian Commission on Safety and Quality in Health Care, 2015), so this was targeted in addition to initial choice

of therapy. Furthermore, a significant reduction in the inappropriate use of the broad spectrum antibiotic ceftriaxone was demonstrated.

As inappropriate use of antimicrobials for prevention and treatment of infections can result in adverse effects such as HCA-CDI, a project examining the relationship between AMS and CDI was conducted (Chapter 4). The purpose of this chapter was to determine whether the combination of a health district-wide ASP and a targeted education and feedback initiative would result in a reduction in HCA-CDI rates. In addition, the burden of HCA-CDI in terms of LOS and hospital costs was investigated. Although a reduction in monthly HCA-CDI rates was observed using ITS analysis, this did not reach statistical significance. A case-control analysis showed that there was a significant burden on the patient in terms of additional length of hospital stay related to HCA-CDI, and also a cost burden for the health service. These findings reinforce the importance of developing AMS strategies to reduce HCA-CDI, including a reduction in inappropriate antimicrobial use (Leffler and Lamont, 2015).

As most of the available literature on AMS outcomes is derived from tertiary metropolitan hospitals (Schuts et al., 2016), there is an evidence gap for programs that can be applied to rural and regional facilities, and multiple hospitals. Chapter 5 reported AMS outcomes from two neighbouring health districts with varying resource levels. A shared strategy of antimicrobial education and restriction was facilitated by a centrally deployed CDSS, demonstrating that technology can be used to support AMS in hospitals with disparate size and locations (Baysari et al., 2016). Antimicrobial use, costs, HCA-CDI, infection-related LOS and mortality were selected as outcomes; those have been

previously reported in the published literature (Baysari et al., 2016). Significant changes to patterns of antimicrobial use were observed, along with reductions in antimicrobial costs and HCA-CDI. Although LOS and mortality were not substantially reduced when compared with background rates, these were included as important balancing measures that may have been negatively impacted by changing patterns of antimicrobial use (Davey et al., 2013; Davey et al., 2017). Some of the initial impact of the shared program diminished over time, suggesting that ongoing novel approaches to AMS education may be required. One such approach in the form of an e-learning tool was described in Chapters 6 and 7.

The challenges of providing continuing health professional education, such as increased clinical demands, resource limitations and competing mandatory online training modules, are further exacerbated in health districts with multiple hospitals spread across a wide geographic area. Use of newer technological approaches to education may provide a solution. Chapter 6 described the design and implementation of a novel educational approach for improving knowledge on use of the anti-MRSA antimicrobial vancomycin. As an online e-learning tool, this approach was well received by users and offered an alternative to resource-intensive face-to-face education. It became evident from survey data that there were shortcomings in clinical vancomycin knowledge, particularly among nurses and doctors. Those shortcomings have provided opportunities to further explore vancomycin education strategies.

Chapter 7 examined the e-learning approach to education, through comparison with an email update to clinicians. Post-intervention knowledge survey scores increased for

nurses following the e-learning tool, but were not significantly different for doctors or pharmacists. This suggests that nurses may be better suited to receiving antimicrobial education in this format. The comparator email was associated with an increase in knowledge survey scores among the total participant group and among doctors. This probably arose from both the shorter time requirement and the didactic nature of the educational e-mail. Those survey participants who used educational resources to answer questions achieved higher scores than those who did not refer to resources. Pharmacists were more likely to achieve higher survey scores than doctors and nurses, thus they are well placed to facilitate additional targeted education to those professional groups. No significant differences were observed at the intervention and comparator sites pre- and post-intervention of therapeutic vancomycin plasma levels.

8.3 Implications

The research described in this thesis has a number of implications. It provides a model for evaluation of an ASP across a rural and regional health district comprising multiple hospitals. Where there are existing political or professional links between hospital sites, the reported quality improvement methodology is pragmatic and transferable to different clinical settings. For example, the research methodology described in Chapter 2 relates to orthopaedic surgery, but could just as easily be applied to other specialties where there is inappropriate antimicrobial prophylaxis. Equally, Chapter 3 relates to CAP, but could be applied to other common treatment indications with clear guidelines and evidence for appropriate antimicrobial use, such as cellulitis or UTIs.

AMR is a real and present global threat to human health (World Health Organisation, 2011). Thus, there is a requirement for culture change in organisations, with the ultimate aim of improving patient outcomes through better antimicrobial use. The work contained in this thesis provides realistic methods for achieving change in culture. Furthermore,, sharing of AMS expertise across hospitals and health districts resulted in improved equity of program resources, such as those projects reported in Chapters 4, 5 and 6.

A current educational strategy for improving clinical knowledge relating to vancomycin has been provided on an open and free website for any person or organisation around the world who wants to use it (Chapters 6 and 7). The sharing of research methods, data and expertise forms part of the culture within Australian AMS networks.

8.4 Strengths

The research described in this thesis has addressed a knowledge gap in antimicrobial stewardship, namely how to successfully implement a strategy for education and evaluation across multiple hospitals sites, incorporating smaller rural and regional hospitals. Different clinical aspects, with a strong grounding in the literature, were addressed in the chapters, and the use of technology was investigated as a means of overcoming barriers to antimicrobial education. In addition, educational approaches were targeted at different organisational levels, including individual, departmental, hospital, health district, and multiple health districts.

Constructed as a thesis by journal compilation, common themes were present through the chapters, and current standards for evaluation methodology were used where appropriate.

An example is ITS analysis, the quasi-experimental evaluation technique described in Chapters 4 and 5.

The reporting of meaningful outcomes is an aspect of current AMS research that requires improvement (Schuts et al., 2016; Davey et al., 2017). Additionally, there is a shortage of standard definitions for outcome measures (Moehring et al., 2017), which creates a barrier to pragmatic AMS research. Although process measures such as antimicrobial use patterns and costs are useful in describing the effectiveness of interventions, the focus should primarily be on patient safety. In this way, AMS becomes firmly embedded within the framework of clinical governance. Outcome measures selected for inclusion in this research project broadly align with a recent expert consensus, based on: association with improved antimicrobial prescribing, improved patient care, utility in targeting AMS efforts, and feasibility for monitoring within an eMR (Moehring et al., 2017). Markers of patient safety were reported in all of the individual research projects: renal function and SSI rates in Chapter 2; 30 day readmission rate and mortality in Chapter 3; CDI and LOS in Chapter 4; CDI, infection related LOS and mortality in Chapter 5; and vancomycin therapeutic levels, as a measure of both treatment effectiveness and drug toxicity in Chapter 7. Chapter 6 reported design and implementation of an e-learning tool, and therefore did not address patient-related outcome measures.

Meaningful statistical significance was achieved in some components of all of the studies. Where possible, qualitative measures were also described (Chapters 3, 4 and 6). Examples included email feedback and qualitative survey responses. This allowed for a more comprehensive understanding of the cultural drivers of hospital antimicrobial use.

8.5 Limitations

Detailed descriptions of limitations relating to the individual research projects were provided in Chapters 2, 3, 4, 5, 6 and 7. There were some overarching limitations, often inherent to pragmatic clinical research projects.

Small sample sizes potentially compromised statistical significance and may have hampered applicability of results to similar populations. The uncontrolled before-and-after intervention study designs necessarily constrained conclusions about the impact of interventions on outcomes. Conclusions on the effect of changes in antimicrobial use on patient outcomes were also impacted by the existence of a complex health system with multiple external confounders, such as community-acquired infections, variations in drug acquisition costs and infection control practices. The retrospective study methodology in Chapter 5 was used as a pragmatic way of assessing outcomes of AMS, where a prospective study would have been unachievable due to parallel clinical commitments during the implementation phase. Antimicrobial resistance was not included as an outcome measure for this research project as a longer ASP timeline would be required to effect meaningful changes to resistance patterns (Yong et al., 2010).

Multisite methodology was one of the strengths of this research with the exceptions of Chapters 2 and 3 where clinical data were only presented from the tertiary referral hospital. This was despite attempts by the candidate to collect data at one or more of the smaller sites. Lack of on-site personnel, and a busy clinical load prevented adequate data

collection. The methodology for those studies remains applicable to a multisite approach, as described in suggestions for future research (Section 8.6).

In the research related to the VI (Chapters 6 and 7), the pre- and post-intervention surveys were not linked, limiting the statistical analysis to grouped comparisons. Also, low survey response rates, particularly post-intervention, hampered conclusions about the effectiveness of the VI. This project was also the only one to compare different educational methods, those being an e-learning tool and an email (Chapter 7).

Assessing the appropriateness of prescribing of antimicrobials according to the recommendations in the Australian *Therapeutic Guidelines: Antibiotic* (Antibiotic Expert Group, 2010) was an important part of this research. Midway through the research, a new version of the *Therapeutic Guidelines: Antibiotic* was released (Antibiotic Expert Groups, 2014). However, there were no changes to the recommendations for antimicrobial use related to the projects described in Chapters 2, 3 or 4. Chapter 5 was a retrospective analysis based on the 2010 version of the guidelines, and Chapters 6 and 7 were constructed around clinical content that was derived only from the 2014 version.

8.6 Suggestions for future research

This research demonstrated changes in antimicrobial use patterns over time, and the effect on patient outcome measures. A number of questions have arisen that can guide further research. The effect of AMS on patterns of antimicrobial resistance at various organisational levels presents novel research opportunities, particularly in the multisite, non-metropolitan setting. As the majority of study methodologies were uncontrolled,

there is also an opportunity to conduct studies with design features that include prospective data collection and randomisation, and further multisite research that can capture data from the smaller rural hospitals. An emerging area in AMS is mixed methods research, whereby qualitative components provide a deeper insight into the effectiveness of interventions and help to inform quantitative evaluation. This would be of particular use in assessing technological advances. There is also the potential to further explore much sought after outcome data such as clinical cure rates and mortality.

8.7 Conclusions

With the increasing prevalence of antimicrobial resistance, there is an urgent need to develop ways to improve use of antimicrobials in humans. In hospitals, where patients are treated for severe and complex infections, antimicrobial stewardship offers a system for improving patient outcomes while addressing antimicrobial resistance at a broader level. In that context, this research has achieved the following meaningful contributions:

- (1) An educational model for discontinuing unnecessary gentamicin use in the setting of orthopaedic surgery was implemented without evident harm to patients.
- (2) An intervention leading to a significant reduction in antimicrobial duration of therapy for patients with community-acquired pneumonia, without any negative impact on 30-day readmission rates and mortality.
- (3) The burden of *Clostridium difficile* infection as a consequence of antimicrobial use was shown by significant increases in patient length of stay and hospital costs.
- (4) A multisite educational model resulted in significant improvements in antimicrobial use and was associated with reductions in *Clostridium difficile* infection, infection-related lengths of stay and mortality.

(5) An innovative educational method in the form of the Vancomycin Interactive e-learning tool identified that different educational strategies can be suited to particular health professionals. Through addressing barriers to traditional educational methods, this freely available online e-learning tool offers a potential model for future antimicrobial education.

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9 Appendices

Appendix A

Literature search methodology

An initial search for the available literature, using a censorship date of 30 June 2013 was employed using the following strategy on Pubmed:

((antimicrobial[ti] OR antifungal[ti] OR antibiotic[ti]) AND (utilisation[ti] OR utilization[ti] OR usage[ti] OR stewardship[ti] OR "management team"[ti]) OR "antimicrobial use"[ti] OR "antibiotic use"[ti] OR "antifungal use"[ti]) OR (("anti-bacterial agents"[MeSH] OR "antifungal agents"[MeSH]) AND "Physician's Practice Patterns"[MeSH])).

As an “antimicrobial stewardship” MeSH term was not available, the search strategy from the recent Cochrane review by Davey and colleagues (2013) was analysed to determine the most closely related MeSH terms, which included “anti-bacterial agents’, “anti-fungal agents” and “Physician's Practice Patterns”. Searches for antiviral agents and other antimicrobials were excluded from this literature review.

Literature for this review was searched for using the following hierarchy (University of Illinois at Chicago, 2013): meta-analyses and systematic reviews; randomised controlled trials; cohort studies; case-control studies; case series, case reports; editorials, expert opinion.

Subsequent searches for the subtopics within the review were analysed from within this search strategy, with a recent review article on each topic acting as a check for completeness of the review. The majority of studies in this field were of low quality

according to the evidence pyramid, mainly consisting of uncontrolled observational before-and-after studies. A 2013 Cochrane review identified 507 full text articles on the improvement of antibiotic prescribing in hospital inpatients (Davey et al., 2013). Of these, 300 were excluded on the basis of the study design, which included inadequate time series analyses and uncontrolled before-and-after studies. Some of these studies were included, because their structure provided insight into the type of projects that were carried out as part of this thesis.

Search terms used for Chapter 2 were: “orthopaedic surgery”, “orthopedic surgery”, “surgical prophylaxis”, “antimicrobial/s”, “antibiotic/s”, “antimicrobial stewardship”, “antibiotic stewardship”, “urinary catheter/s”, “catheter-associated bacteriuria”, “urinary tract infection/s”, and “prophylaxis”.

Search terms used for Chapter 3 were: “community-acquired pneumonia”, “antimicrobial stewardship”, “antimicrobial/s”, and “antibiotic/s”.

Search terms used for Chapter 4 were: “*Clostridium difficile*”, “antibiotic/s”, “antimicrobial/s”, “proton pump inhibitor/s”, “length of stay”, “health costs”, “antimicrobial stewardship”, and “antibiotic stewardship”.

Search terms used for Chapter 5 were: “antimicrobial/s”, “*Clostridium difficile*”, “length of stay”, “health costs”, “multisite”, “multi-site”, “mortality”, “antimicrobial stewardship”, and “antibiotic stewardship”.

Search terms used for Chapters 6 and 7 were: “nursing education”, “pharmacy education”, “medical education”, “continuing education”, “vancomycin”, “antimicrobial stewardship”, “online learning”, and “serious game”.

References

- Davey, P, Brown, E, Charani, E, Fenelon, L, Gould, IM, Holmes, A, Ramsay, CR, Wiffen, PJ & Wilcox, M 2013. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*, 4, CD003543.
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Appendix B

Ethics materials and data collection form reported in Chapter 2.

RENEWAL APPROVAL

In reply please quote: HE11/103

Further Enquiries Ph: 4221 3386

10 September 2013

Mr Stuart Bond
Pharmacy Department
LMB 8808
South Coast Mail Centre
Wollongong NSW 2521
Dear Mr Bond

I am pleased to advise that renewal of the following Human Research Ethics application has been approved. A copy of this advice has been forwarded to the ISLHD for their records.

Ethics Number: HE11/103

AuRED Number: LNR/11/WGONG/103

Project Title: An audit of the choice, timing and duration of antibiotic prophylaxis in orthopaedic surgery patients at a regional teaching hospital

Name of Researchers: Mr Stuart Bond, Dr Craig Boutlis

Approved From: 15 September 2013

Expiry Date: 14 September 2014

Please note that approvals are granted for a twelve month period. Further extension will be considered on receipt of a progress report prior to expiry date.

This certificate relates to the research protocol submitted in your original application and all approved amendments to date. Please remember that in addition to completing an annual report the Human Research Ethics Committee also requires that researchers immediately report:

- proposed changes to the protocol including changes to investigators involved
- serious or unexpected adverse effects on participants
- unforeseen events that might affect continued ethical acceptability of the project.

Yours sincerely



Professor Jim Greenstein
Chair, UOW & ISLHD Health and Medical
Human Research Ethics Committee

Ethics Unit, Research Services Office
University of Wollongong NSW 2522 Australia
Telephone (02) 4221 3386 Facsimile (02) 4221 4338
Email: rso-ethics@uow.edu.au Web: www.uow.edu.au

Orthopaedic surgical prophylaxis project data collection form

Bed	Name	MRN	Opn	Surgeon and Reg	OpDate	MSU Preop (MRSA?)	Cr Pre	Cr Pst	Date	ABx – In/Pre (Wt)	ABx – Out/Post

Appendix C

Ethics materials and data collection form reported in Chapter 0.

RENEWAL APPROVAL

In reply please quote: HE11/377

Further Enquiries Ph: 4221 3386

10 September 2013

Mr Stuart Bond
Pharmacy Department
LMB 8808
South Coast Mail Centre
Wollongong NSW 2521
Dear Mr Bond

I am pleased to advise that **renewal** of the following Human Research Ethics application has been **approved**. A copy of this advice has been forwarded to the ISLHD for their records.

Ethics Number:	HE11/377
AuRED Number:	LNR/11/WGONG/115
Project Title:	An audit of antibiotic prescribing for community-acquired pneumonia in the Emergency Department
Name of Researchers:	Mr Stuart Bond, Dr Craig Boutlis
Approved From:	29 September 2013
Expiry Date:	28 September 2014

Please note that approvals are granted for a twelve month period. Further extension will be considered on receipt of a progress report prior to expiry date.

This certificate relates to the research protocol submitted in your original application and all approved amendments to date. Please remember that in addition to completing an annual report the Human Research Ethics Committee also requires that researchers immediately report:

- proposed changes to the protocol including changes to investigators involved
- serious or unexpected adverse effects on participants
- unforeseen events that might affect continued ethical acceptability of the project.

Ethics Unit, Research Services Office
University of Wollongong NSW 2522 Australia
Telephone (02) 4221 3386 Facsimile (02) 4221 4338
Email: rso-ethics@uow.edu.au Web: www.uow.edu.au

1a. Patient audit number: _____ 1b. MRN: _____ 1c. Site: _____

2. Initials (eg. JoSm): First __ Last __

3a. Date of birth: _____ 3b. Sex: M F

4a. Arrival date: _____ 4b. Arrival time: _____ 4c. Admitted: Y N U

Exclusion criteria:

< 18 years of age

Immunosuppressed (HIV positive or concurrent chemo/immunosuppressant therapy)

Cystic fibrosis

Bronchiectasis

Exacerbation of COPD or asthma if not involving pneumonia

Suspected or confirmed tuberculosis

Aspiration or hospital-acquired pneumonia

Discharged from hospital within the previous 14 day period

Patients transferred from another hospital

5. Placement after ED: Discharge HITH Ward ICU/HDU Transfer
Other

Doctor's diagnosis: Pneumonia Chest infection Other: _____
Unknown

Dr's assessment of severity: Mild Moderate Severe Unknown

CAP confirmed on Chest X-ray report: Yes Equivocal No Not done
Unknown

SMART-COP severity score (on first observations):

		Result	Score
S	systolic BP < 90mmHg (2 points):		
M	multilobar involvement (1 point):		
A	albumin < 35g/L (1 point)		
R	respiratory rate 25br/min or more (30br/min in >50yrs) (1 point)		
T	tachycardia 125bpm or more (1 point)		
C	confusion (acute) (1 point)		
O	Oxygen low- PaO ₂ <70 (<60 for over 50yrs) O ₂ sat 93% or less (90% or less for > 50 yrs)(2 pts)		
P	pH < 7.35 (2 points)		
SMART-COP score (greater than or equal to 5 = severe)			

Symptoms: Cough – Y N U Sputum – Y N U Fever – Y N U
Dyspnoea – Y N U

Severity score documented: Y N Unknown Which score/result:

Sputum sample taken: Yes No Unknown

Sputum result: Pathogen(s)_____ Negative Contaminated

Allergies/Adverse drug reactions _____

Type of reaction: _____

Antibiotics given prior to ED (or “none”): _____

Initial antibiotic regimen

Antibiotic	Dose	Frequency	Correct, Low, High, Unclear	Route	Right drug? *	ID/micro approved?

* Completely, Partially, Not at all, Unclear

Antibiotic: who ordered it: AMO AMO'sReg AMO'sJMO EDCons EDReg
EDJMO Unk

Who charted it: AMO AMO'sReg AMO'sJMO EDCons EDReg
EDJMO Unk

Medication changed by team: Yes No Unk Date: _____ To what:

20a. Total duration ABx in hospital: _____ days 20b. Days of ABx given at D/C:
_____ days

21a. Discharge date: _____ 21b. Date of death (if applicable):

22. Final diagnosis/es: _____

23. Comments: _____

Appendix D

Ethics materials and data collection form reported in Chapter 4.

APPROVAL

In reply please quote: HE13/137
Further Enquiries Ph: 4221 3386

26 April 2013

Mr Stuart Bond
Pharmacy Department
LMB 8808
South Coast Mail Centre
Wollongong NSW 2521

Dear Mr Bond,

Thank you for your response to the HREC letter regarding the ethics application below. I am pleased to advise that the application has been approved. Before you can proceed with the project you must first have authorisation from the relevant NSW Ministry of Health Local Health District.

Ethics Number: HE13/137
AuRED Number: LNR/13/WGONG/28
Project Title: Evaluation of the Antimicrobial Stewardship Program in Illawarra Shoalhaven Local Health District
Researchers: Mr Stuart Bond, Dr Craig Boutlis
Sites/CIs approved:

Site	Principal Investigator for site
Wollongong Hospital	Mr Stuart Bond
Shellharbour Hospital	Mr Stuart Bond
Shoalhaven District Hospital	Mr Stuart Bond
Bulli Hospital	Mr Stuart Bond
Port Kembla Hospital	Mr Stuart Bond
Milton-Ulladulla Hospital	Mr Stuart Bond
Coledale Hospital	Mr Stuart Bond
Kiama Hospital	Mr Stuart Bond

Ethics and Research Services Office
University of Wollongong NSW 2522 Australia
Telephone: (02) 4221 3386 Fax: (02) 4221 4333
Email: ethics@uow.edu.au Web: www.uow.edu.au/ethics

Clostridium difficile project data collection form

1a. Patient audit number: _____ 1b. Site: _____

2a. Initials (eg. JoSm): First _ _ Last _ _ 2b. MRN: _____

3a. Date of birth: _____ 3b. Sex: M F Other

4a. Date admitted: _____ 4b. Date discharged: _____

5a. Admitting consultant: _____ 5b. Unit: _____

6a. Date of diagnosis: _____ 6b. Micro Episode no. _____

7a. Was C. diff diarrhoea the reason for admission? Y / N / U

7b. If NO, reason: _____

8. Date of discharge for most recent admission (if applicable): _____

9. Primary classification: a. HCA-inpatient b. HCA-outpatient definite (within 4 weeks of discharge)

c. HCA-O probable (4-8 weeks) d. HCA-O possible (8-12 weeks) e. Nursing home f. Community

10. If health care associated: a. Hospital of likely origin _____ b. Ward: _____

c. Consultant: _____ d. Unit: _____

11. Potential risk factors Y/N/U Drug + dose + indication/procedure if Yes

a. Current PPI use _____

b. Current H2 antagonist _____

c. Antiperistaltic use _____

d. GI surgery within 30 days _____

12. Co-morbidities Y/N/U

a. Current malignancy _____

b. Immunosuppressive drugs _____

c. Immunosuppressive illness _____

13. Other important risk factors / co-morbidities / contributory factors

14. Current antibiotic use

a. Antibiotic use at time of diagnosis		Y / N / U
b. Name of antibiotic	IV/Oral	Dose/Frequency/Duration
Indication		
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

15. Previous antibiotic use

a. Antibiotic use 1 month prior to diagnosis		Y / N / U
b. Name of antibiotic	IV/Oral	Dose/Frequency/Duration
Indication		
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

c. If off antibiotics at diagnosis, date last antibiotic stopped:

16. Initial Treatment

a. Drug	IV/Oral	Date started
Dose/Frequency/Intended duration		
_____	_____	_____
_____	_____	_____
_____	_____	_____

17a. Did AMS recommend changing treatment? Y / N / U

17b. AMS-recommended treatment

a. Drug	IV/Oral	Date started
Dose/Frequency/Intended duration		

_____	_____	_____

_____	_____	_____

_____	_____	_____

18. Were other antibiotics withdrawn within 48 hours of diagnosis?

a. Completely (stat) b. Completely (< 48hrs) c. Partially d. Changed e. Not at all f. Unknown

19a. ICU required? Y / N / U

19b. Surgery required? Y / N / U

20. Mortality

a. 7 days: Alive / Died / Unk b. Discharge: Alive / Died / Unk c. 30 days: Alive / Died / Unk

21. Comments

Please return to Stuart Bond, Pharmacy, 4222 5646 or pager #263

Appendix E

Ethics materials reported in Chapter 5.

RENEWAL APPROVAL - ISLHD AUTHORISATION

In reply please quote: HE13/137

Further Enquiries Ph: 4221 3386

14 March 2014

Mr Stuart Bond
Pharmacy Department
LMB 8808
South Coast Mail Centre
Wollongong NSW 2521

Dear Mr Stuart Bond

I am pleased to advise that renewal of the following Human Research Ethics application has been approved.

Ethics Number:	HE13/137
AuRED Number:	LNR/13/WGONG/28
Project Title:	Evaluation of the Antimicrobial Stewardship Program in Illawarra Shoalhaven Local Health District
Name of Researchers:	Mr Stuart Bond, Dr Craig Boutlis
Renewed From:	23 April 2014
Expiry Date:	22 April 2015

Please note that approvals are granted for a twelve month period. Further extension will be considered on receipt of a progress report prior to expiry date.

This certificate relates to the research protocol submitted in your original application and all approved amendments to date. Please remember that in addition to completing an annual report the Human Research Ethics Committee also requires that researchers immediately report:

- proposed changes to the protocol including changes to investigators involved
- serious or unexpected adverse effects on participants
- unforeseen events that might affect continued ethical acceptability of the project.

A copy of this advice has been forwarded to the ISLHD for their records.

Yours sincerely

Associate Professor Sarah Ferber
Chair, UOW & ISLHD Health and Medical
Human Research Ethics Committee

cc: Governance Officer, Research Directorate, ISLHD

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AMENDMENT APPROVAL - ISLHD

In reply please quote: HE13/137
Further Enquiries Phone: 4221 3386

9 September 2015

Mr Stuart Bond
Pharmacy Department
LMB 8808
South Coast Mail Centre
Wollongong NSW 2521

Dear Mr Bond,

I am pleased to advise that the amendments dated 3 September 2015 to the following Human Research Ethics application have been approved.

Ethics Number: HE13/137
AuRED Number: LNR/13/WGONG/28
Project Title: Evaluation of the Antimicrobial Stewardship Program in Illawarra Shoalhaven Local Health District
Name of Researcher/s: Mr Stuart Bond, Dr Craig Boutlis, A/Professor Spiros Miyakis, Adriana Chubaty, Brendan McMullan, Dr Pam Konecny, Suman Adhikari, Kate Clezy, Mona Mostaghim

Sites/CIs reviewed:

Site	Principal Investigator for site
Wollongong Hospital	Mr Stuart Bond
Shellharbour Hospital	Mr Stuart Bond
Shoalhaven District Memorial Hospital	Mr Stuart Bond
Bulli Hospital	Mr Stuart Bond
Port Kembla Hospital	Mr Stuart Bond
Milton-Ulladulla Hospital	Mr Stuart Bond
Coledale Hospital	Mr Stuart Bond
Kiama Hospital	Mr Stuart Bond
David Berry Hospital	Mr Stuart Bond
St George Hospital	Mr Stuart Bond
Prince of Wales Hospital	Mr Stuart Bond
Sydney children's Hospital	Mr Stuart Bond
Sutherland Hospital	Mr Stuart Bond

Appendix F

Ethics materials reported in Chapter 6 and Chapter 7.

APPROVAL

In reply please quote: HE15/005

Further Enquiries Ph: 4221 3386

14 January 2015

Mr Stuart Bond
Pharmacy Department
LMB 8808
South Coast Mail Centre
Wollongong NSW 2521

Dear Mr Bond,

I am pleased to advise that the Human Research Ethics application referred to below has been approved. Before you can proceed with the project you must first have authorisation from the relevant NSW Ministry of Health Local Health District.

Ethics Number: HE15/005
AuRED Number: LNR/15/WGONG/2
Project Title: Analysing the effect of an interactive learning module on health professionals' knowledge of vancomycin dosing, administration and monitoring
Name of Researcher/s: Mr Stuart Bond, Mrs Shelley Crowther
Sites/CIs reviewed:

Site	Principal Investigator for site
ISLHD	Mr Stuart Bond

Documents Reviewed/Approved: NSW LNR (submission code: AU/6/6B7C116)
Vancomycin Knowledge Survey

Approval Date: 13 January 2015

Expiry Date: 12 January 2016

The University of Wollongong/ISLHD Health and Medical HREC is constituted and functions in accordance with the NHMRC *National Statement on Ethical Conduct in Human Research*. The HREC has reviewed the research proposal for compliance with the *National Statement* and approval of this project is conditional upon your continuing compliance with this document.

A condition of approval by the HREC is the submission of a progress report annually and a final report on completion of your project. The progress report template is available at <http://www.uow.edu.au/research/rso/ethics/UOW009385.html>. This report must be completed, signed by the appropriate Head of School and returned to the Research Services Office prior to the expiry date.

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